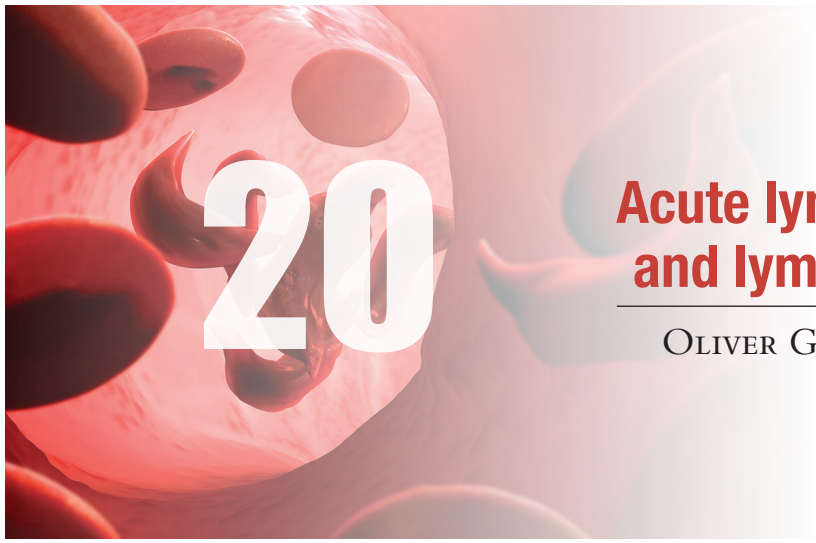

20 Acute lymphoblastic leukemia and lymphoblastic lymphoma

Oliver G. Ottmann and Liora Schultz

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common leukemia in children (representing 23% of all pediatric cancer diagnoses and 76% of leukemias among children <15 years of age) but accounts for only 20% of adult acute leukemias. Lymphoblastic lymphoma (LBL) is rarer, representing 2% of adult and 30% of pediatric non-Hodgkin lymphomas. These entities are closely related biologically and clinically and may share presenting features, although symptoms of bone marrow dysfunction are much more common in ALL. The distinction between ALL and LBL relies on percentage of bone marrow lymphoblasts, with bone marrow involvement exceeding 20% classified as ALL and bone marrow involvement of <20% classified as LBL. Due to overlapping biology, in 2017, the World Health Organization (WHO) reclassified LBL as Burkitt lymphoma/leukemia (B-ALL)/lymphoblastic lymphoma in the pediatric and adult setting, and therapy for LBL is now guided by principles of acute lymphoblastic leukemia treatment, rather than non-Hodgkin lymphoma.

The prognosis for both adult and especially childhood ALL has improved substantially since the beginning of multiagent curative therapy in the 1970s, driven by clinical studies employing increasingly intensive combination chemotherapy regimens administered in a risk-directed manner and including central nervous system (CNS) prophylaxis. In children, treatment now results in complete remission (CR) rates of 97%-99%, 5-year event-free survival (EFS) rates of 80%-87%, and 5-year survival rates of 90%-94%. Adoption of pediatric or pediatric-inspired intensive treatment regimens have improved the prognosis of adolescents and adults with CR rates of up to 95% and 5-year survival rates approaching 70% but have not eliminated the negative prognostic impact of age. In patients older than about 45 years, administration of these intensive regimens becomes increasingly difficult because of toxicity and comorbidities, resulting in substantially inferior outcome. In addition, advancing age is associated with a genetic risk profile that becomes increasingly skewed towards high-risk groups. As consequence, responses to remission induction therapy are less deep, as evidenced by higher level of minimal (more recently rephrased as "measurable") residual disease (MRD) following initial treatment cycles. Highly sensitive MRD assessment has become a transformational approach to patient management by partially or completely replacing conventional risk classification algorithms and guiding

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treatment decisions, including referral for allogeneic hematopoietic stem cell transplantation (HSCT). In addition, a growing armamentarium of newer immuno-oncology agents targeting surface antigens expressed on leukemic blasts are revolutionizing our approach to frontline and salvage therapy for B-cell precursor ALL and are beginning to change current treatment paradigms that rely on cytotoxic chemotherapy and HSCT. More detailed molecular genetic characterization at diagnosis has delineated new ALL subgroups with therapeutically actionable targets such as gene fusions involving kinases. The impressive dynamics with which the field of ALL is progressing relies on the majority of patients being treated in prospective clinical trials, most of which are conducted by pediatric or adult cooperative study groups. Moreover, the prognosis of individual patients is improved when treatment occurs in an experienced center within a clinical trial.

Classification and diagnosis of acute lymphoblastic leukemia

WHO classification

The WHO classification, revised several times (fourth edition, 2017), has replaced the older French-American-British classification based on morphology and reflects the increased understanding of the biology and molecular pathogenesis of the diseases. The WHO classification divides these heterogeneous lymphoid diseases into 2 major categories: precursor lymphoid neoplasms and mature lymphoid neoplasms. The precursor lymphoid diseases include both B-lymphoblastic leukemia/lymphoma and T-lymphoblastic leukemia/lymphoma. The WHO classification further subdivides the precursor B-cell ALL cases by recurring molecular-cytogenetic abnormalities to provide prognostic and therapeutic information as well as to facilitate the implementation of specific molecularly targeted therapies (Table 20-1). Burkitt lymphoma/leukemia is the one subset of ALL that is classified as a mature B-lymphoid neoplasm.

The distribution of the immunophenotypic subsets differs slightly between adult and pediatric ALL. T-cell ALL accounts for <10% of children below age 10 and increases with age during adolescence and constitutes approximately 25% of adult ALL, though its incidence decreases again with increasing age. Mature B-cell/Burkitt ALL accounts for ~2%-5% of adult and pediatric ALL cases, and B-cell precursor (BCP)-ALL accounts for the remaining cases. There are also racial or ethnic differences in the distribution, with T-cell ALL accounting for 10%-12% of White and 25% of Black children with ALL.

Table 20-1 WHO classification of precursor lymphoid neoplasms (B- and T-lymphoblastic leukemia/lymphoma)

B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B lymphoblastic leukemia/lymphoma with t(9:22)(q34;q11.2); *BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23); *KMT2A*★ rearranged
B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy†
B-lymphoblastic leukemia/lymphoma with hypodiploidy‡
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19) (q23;p13.3); E2A-PBX1(TCF3-PBX1)
B-lymphoblastic leukemia/lymphoma with *iAMP21*
B-lymphoblastic leukemia/lymphoma *BCR-ABL1*-like§
T-lymphoblastic leukemia/lymphoma
NK-lymphoblastic leukemia/lymphoma‖

★Formerly known as *MLL*.

†>50 chromosomes and usually <66 chromosomes.

‡<46 chromosomes, often subdivided into hear haploid (23-29 chromosomes), low hypodiploid (33-29), high hypodiploid (40-43), near diploid (44-45). The last category is sometimes not counted as hypodiploid.

§"Provisional entity."

‖Rare entity, difficult to distinguish from blastic plamocytoid dendritic neoplasms, some early T-cell or even AML entities with few distinguishing markers. Not discussed further.

Diagnostic workup

Examination of a bone marrow aspirate is important in the diagnostic evaluation of suspected ALL because as many as 10% of patients with ALL lack circulating blasts at the time of diagnosis and because bone marrow cells tend to yield more robust characterization than blood cells for genetic studies. Fibrosis or tightly packed marrow can occasionally lead to difficulties with marrow aspiration and can necessitate a biopsy to make the diagnosis. In patients with marrow necrosis (<2% of cases), patchy disease or aplastic presentation, multiple and repeated marrow aspirations are sometimes needed to obtain diagnostic tissue. In pediatric patients with elevated circulating lymphoblasts, the diagnosis can be made using peripheral blood. Peripheral blood is particularly useful in subsets of high-risk patients unable to tolerate bone marrow procedures (ie, mediastinal mass, pediatric patients unable to tolerate anesthesia). Peripheral blood provides a noninvasive diagnostic approach, with immunophenotype expected to overlap across bone marrow and peripheral blood diagnostic specimen.

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The process of classifying ALL involves a multiparametric approach where cumulative tests with increasing specificity from the surface of the cell to the genome yield the specific diagnostic characteristics of an individual's leukemia and accompanying risk stratification. Critical diagnostic assessments include:

- Morphology
- Immunophenotyping
- Identification of genetic aberrations

The initial diagnostic step is identifying lymphoblasts in the bone marrow or peripheral blood. Morphologic assessment is based on pathologic review of how cellular features, including the nucleus and cytoplasm, physically appears under the microscope. Morphologic assessment cannot always differentiate lymphoblastic disease from myeloid disease, nor T-lymphoblastic disease from B-lymphoblastic disease, and therefore lacks specificity in its diagnostic merit. Upon gross recognition of morphologically atypical cells, immunophenotyping and genetic analyses are pursued to further narrow and characterize the specific leukemia subtype. Immunophenotype utilizes flow cytometry (FC) to survey a panel of surface and intracellular markers, including canonical lymphoid, myeloid, B and T-cell markers. Genetic analyses include conventional karyotyping, fluorescence in situ hybridization (FISH), and qRT-PCR for detection of the $p190^{BCR\text{-}ABL1}$ or $p210^{BCR\text{-}ABL1}$ transcripts in Philadelphia chromosome–positive ALL. Targeted next-generation sequencing (NGS) with lymphoid panels is being used with increasing frequency and may replace cytogenetic analyses. Gene fusion assays and low-density arrays have the purpose of identifying patients with Ph-like ALL, for which the diagnostic algorithms have not yet been standardized, however. Characterization of the leukemia genome enables identification of specific genetic driver mutations and genetic features known to be responsive to targeted agents, and provides prognostic information.

Immunophenotyping

Flow cytometry

Because the morphologic and cytochemical features of leukemic lymphoblasts are not specific enough for all important diagnostic distinctions, immunophenotyping by FC is essential for diagnosis. A panel of antibodies is needed to establish the diagnosis and to distinguish among the different immunologic subclasses of leukemic cells. Although ALL can be classified according to the normal sequential stages of normal T-cell and B-cell development, most groups find it therapeutically useful to distinguish only between T-cell ALL, B-cell precursor lymphoblastic ALL, and mature B-cell ALL.

Cytoplasmic CD3 is lineage-specific for T cells, which are also positive for terminal deoxynucleotidyl transferase (TdT) and frequently for the less specific marker CD7. B-lineage cells are distinguished by a combination of at least 2 of CD19, cCD79a, or cCD22. Mature B cells are surface immunoglobulin positive and most are also CD20 positive. In addition, many precursor ALLs are CD10-positive B-lineage cells positive for HLA-DR and TdT and both B- and T-lineage cells frequently express CD38. A summary of CD markers and specific immunophenotypic techniques and findings in ALL is found in Chapter 12. While an often more limited panel of canonical B and T-cell differentiation markers has traditionally also been used for immunophenotyping at relapse, surface marker expression may nowadays be influenced by prior exposure to immunotherapy targeting specific antigens such as CD19. Downregulation of CD19 and CD22 at relapse is becoming more common after treatment with several now commercially available immunotherapy modalities (CD19 or CD22 targeting chimeric antigen receptor [CAR] T cells, blinatumomab, inotuzumab) so that immunophenotyping panels can no longer rely upon these antigens to define a B-cell tumor phenotype.

Immunophenotypes in clinical and genetic subgroups

One of the clinically most relevant distinctions made by FC is between B-cell precursor ALL (BCP-ALL) and mature B-cell ALL or Burkitt ALL, which has a unique immunophenotype with expression of surface immunoglobulin, strong expression of CD20, and negativity for TdT. Treatment for mature B-ALL and Burkitt lymphoma is very different from that of BCP-ALL so the distinction is critical. While mature B-ALL also has distinctive morphologic features with very basophilic, vacuolated blasts (L3 morphology), definitive diagnosis requires confirmation by immunophenotyping. These ALLs are associated with chromosome 8 translocations involving the *MYC* proto-oncogene.

Infants with ALL, typically with genetic rearrangement of the *KMT2A* gene, usually lack CD10 expression, and the genetic aberration associates with a worse prognosis.

Myeloid-associated antigens may be expressed on otherwise typical lymphoblasts and are associated with common genetic variants such as *KMT2A* rearrangements, *ETV6-RUNX1* fusion, Philadelphia chromosome–positive (Ph^+) ALL, and the recently described group with *ZNF384* rearrangements. The presence of myeloid-associated antigens lacks prognostic significance but can be useful in immunologic monitoring of patients for minimal residual leukemia.

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Early T-cell precursor (ETP)-ALL has a unique immunologic signature (typically $CD3^+$, $CD7^+$; $CD8^-$, $CD1a^-$, CD5 weak, and positive for 1 or more stem cell or myeloid antigens) and gene expression profile is reminiscent of a double-negative thymocyte that retains the ability to differentiate into T-cell and myeloid, but not B-cell, lineages. Clinical characteristics include more frequent chromosomal abnormalities, a higher a higher bone marrow (BM) blast count, and a higher risk of CNS involvement at diagnosis compared with non–ETP-ALL/LBL. These cases were initially associated with a dismal treatment outcome with chemotherapy, but recent reports suggest that the adverse outcome may be limited to a higher incidence of induction failure, whereas postinduction outcome may be similar to non-ETP cases with intensive chemotherapy stratified according to MRD. In contrast, ETP-ALL in adult patients appears to have a less favorable prognosis due to lower CR rates and inferior overall survival (OS) compared to patients with non-ETP-ALL/LBL, but small numbers hamper detailed interpretation.

Genetic aberrations in the leukemic cells and their prognostic importance

It is commonly agreed that ALL arises from a lymphoid progenitor cell that has sustained multiple specific genetic injuries that lead to malignant transformation and proliferation. Initially these genetic changes were discovered as recurrent cytogenetic aberrations, but, as molecular techniques have been developed, a multitude of submicroscopic changes have been discovered, and a range of different complementary methodologies are now used for characterization of the leukemic clone.

Compilations of results from multiple studies have, over the years, defined a set of common, nonoverlapping genetic alteration groups that are now regarded as separate subtypes of ALL. More than 75% of adult and childhood cases can readily be classified into prognostically or therapeutically relevant subgroups based on the modal chromosome number (or DNA content estimated by flow cytometry), structural mutations, or expression patterns. Table 20-2 lists selected genetic abnormalities, most of which can be identified by conventional cytogenetic analysis and/or FISH with prognostic and therapeutic relevance.

Genetic changes associated with BCP-ALL

Chromosomal changes: ploidy

Hyperdiploidy (also known as high hyperdiploid), defined as involving 51 to 67 chromosomes, is seen in approximately 25% to 30% of childhood cases and in 6% to 7% of adult cases and is associated with a favorable prognosis in childhood ALL and in some studies of adult ALL. High-hyperdiploid karyotype may be associated with an increased cellular accumulation of methotrexate and its polyglutamates, an increased sensitivity to antimetabolites, and a marked propensity of these cells to undergo apoptosis.

By contrast, hypodiploidy with <44 chromosomes, especially near haploidy (24-31 chromosomes) and low hypodiploidy (32-39 chromosomes), is consistently associated with an adverse prognosis in both children and adults with ALL. Hypodiploidy is uncommon in both children and adults, accounting for <2% of cases. Among children with hypodiploid ALL, near-haploid ALL cases frequently have alterations targeting receptor tyrosine kinase signaling and Ras signaling (71%), and low-hypodiploid cases are characterized by alterations in *TP53* (91%). Between 40% and 50% of patients with TP53 alterations in low-hypodiploid ALL are found to have germline TP53 mutations, indicating underlying cancer predisposition (Li Freumeni Syndrome), and necessitating further investigation for underlying familial cancer predisposition syndrome and appropriate genetic counseling and cancer screening. An additional implication is that patients with high-risk hypodiploid ALL may require allogeneic stem cell transplantation as part of their treatment and caution must be taken to screen and ensure that sibling/related donors do not carry an underlying TP53 mutation.

Intrachromosomal amplification of chromosome 21

The intrachromosomal amplification of chromosome 21 (iAMP21) subgroup of BCP-ALL is one of the newly defined WHO subgroups occurring in 2% of older children and very rarely in adults. It is generated via breakage-fusion-bridge cycles and chromothripsis. The result is the amplification of 1 part of chromosome 21 and loss of other regions. The amplified part always contains the *RUNX1*-gene, which may serve as a marker and a diagnostic tool, which is easily detectable by FISH and array analysis. Patients treated with standard-intensity regimens have fared poorly and have a very high risk of relapse, but stratification to intensive therapy has improved the outcome.

Molecular aberrations: gene rearrangements and deletions

Specific reciprocal translocations have important biologic and clinical significance. Some translocations can mobilize strong promoter-enhancer elements like the immunoglobulin heavy- or light-chain gene or the T-cell antigen receptor

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Table 20-2 Clinical and biologic characteristics of selected genetic subtypes of ALL

Genetic abnormality	Frequency, %		Estimated event-free survival, %		Therapeutics
	Adult	Pediatric	Adult	Pediatric	
B cell					
Hyperdiploidy (>50 chromosomes)	6-7	23-29	30-50 at 5 years	80-90 at 5 years	Antimetabolites
Hypodiploidy (<44 chromosomes)	2	1	10-20 at 3 years	30-40 at 3 years	
t(12;21)(p13;q22)/*ETV6-RUNX1* fusion	0-3	20-25	Unknown	85-95 at 5 years	Intensive asparaginase
t(1;19)(q23;p13.3)/*TCF3-PBX1* fusion	2-3	4-5	40-70 at 3 years	85-90 at 5 years	High-dose methotrexate
t(9;22)(q34;q11)/*BCR-ABL1* fusion	25-30	2-3	40-60 at 2 years	70 at 5 years (DFS)	ABL1 tyrosine kinase inhibitors
t(4;11)(q21;q23)/*KMT2A -AF4* fusion	3-7	2	10-20 at 3 years	30-40 at 5 years	Several principles tested, HSCT
BCR-ABL1–like/Ph-like	Unknown	15-20	Unknown	40-50 at 5 years	Tyrosine kinase (ponatinib)/ JAK2 inhibitors in some cases
iAMP21	Unknown	2	Unknown	60-70 at 5 years	HR therapy
DUX4-rearrangements (+/− associated ERG-deletions)	5-10	4-5	Unknown	ERG-del "favorable"	Unknown
ETV-RUNX1-like	Unknown	1-3	Unknown	"Few relapses"	Unknown
ZNF384 rearrangements	4-11	1-6	Unknown	Unclear/mixed	Unknown
MEF2D rearrangements	5	1-4	Unknown	72	Unknown
T cell					
NOTCH1 mutations	60-70	50	~50 at 4 years	90 at 5 years	γ-Secretase inhibitors
HOX11 overexpression	30	7	70-80 at 3 years	90 at 5 years	
HOX11L2	13	20	~20 at 2 years	~45 at 5 years	
t(9;9)(q34;q34)/*NUP214-ABL1* fusion	5	4	Unknown	Unknown	ABL kinase inhibitors
t(8;14); t(2;8); t(8;22); *c-MYC* overexpression	5	2	50-80 at 3 years	75-85 at 3 years	Short-term intensive multiagent chemotherapy with rituximab

genes to sites adjacent to a variety of genes resulting in deregulated overexpression. Such translocations occur in 2% to 3% of B-precursor ALL; the most frequently affected overexpressed gene is *CRLF2*. Another classic example of this type of translocation occurs in Burkitt ALL, in which the transcription factor *MYC* is translocated to the promoter-enhancer element of the immunoglobulin heavy or light chain and, consequently, is expressed aberrantly.

The genetic rearrangements may also result in the fusion of 2 genes to form a new oncoprotein, which sometimes has dysregulated transcription factor properties. These chimeric transcription factors may regulate genes involved in the differentiation, self-renewal, proliferation, and drug resistance of hematopoietic stem cells. Included in this group of translocations are those involving the *KMT2A* gene (formerly *MLL*) on chromosome 11q23, the most common of which is t(4;11), which results in the creation of the *KMT2A-AF4* fusion gene.

Fusion genes that result in the aberrant activation of tyrosine kinases likewise play a critical role in pathogenesis of ALL subsets. An important example of this type of translocation is the Philadelphia chromosome, where the t(9;22) results in the *BCR-ABL1* fusion gene and causes constitutive activation of the ABL1 tyrosine kinase, which is directly linked to disease pathogenesis and a worse prognosis. The t(9;22) is highly age-dependent, with children representing 2%-3% of patients, but with an increasing incidence with age so that about 25% of adults and 50% of patients >60 years old are Ph^+. The cornerstone of therapy for Ph^+ disease is tyrosine kinase inhibition, with details and outcomes discussed in the following. Additional examples of gene fusions associated with kinase activation are provided in the section on Philadelphia-like ALL.

Further specific fusion-forming translocations involve the *TCF3* locus on chromosome 19. Approximately 3% of children and 6% of adults harbor the t(1;19), resulting

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in a *TCF3-PBX1* fusion; very rarely the t(17;19) produces the *TCF3-HLF* fusion gene. It characteristically has a pre-B immunophenotype. *TCF3-PBX1* was previously associated with poor prognosis, but recent studies have shown excellent results with modestly intensive therapy. However, the prognosis after relapse is very poor. The *TCF3-HLF* cases, on the other hand, have a universally dismal prognosis.

An important translocation resulting in a gene fusion that is almost always submicroscopic is the *ETV6-RUNX1* fusion. This alteration occurs in approximately 20% of childhood cases but is exceedingly rare in adulthood and associates with improved outcome. Deletion or mutation of the IKZF1 gene encoding Ikaros, a transcription factor and tumor suppressor critically involved in B-cell development, is observed in approximately 15% of pediatric and up to 50% of adult patients with BCP-ALL. Various types of lesions exist, most of which result in haploinsufficiency or loss of the DNA-binding domain and a dominant-negative effect. There is a predilection for IKZF1 aberrations in high-risk ALL, in particular Ph-positive and Ph-like BCP-ALL. Numerous studies have shown that IKZF1 deletions are an independent predictor of poor outcome. The prognostic impact of IKZF1 lesions is influenced by the presence or absence of co-occurring recurrent lesions such as the lymphoid transcription factors PAX5 and EBF1 and the transcriptional cofactor BTG1. A molecular profile termed IKZF1plus, defined by the co-occurrence of an IKZF1 deletion with gene deletions in 1 or more of the genes CDKN2A, homozygous CDKN2B, PAX5 or PAR1, in the absence of ERG deletion. This profile confers an extremely high adverse risk and may refine risk stratification in addition to MRD.

More recently, the application of genome-wide analysis of gene expression and DNA copy number, complemented by high-throughput sequencing technologies (transcriptome sequencing [mRNA-seq], targeted exome capture, and whole-genome sequencing) and epigenetic approaches, has identified some novel genetic alterations, further reducing the number of cases with unknown genetic background. One such group was initially identified by a distinct expression pattern linked to deletion of the *ETS*-related gene *ERG*. It was subsequently discovered that the *ERG*-deletions were sometimes subclonal like other copy number alterations, but that the consistent underlying genetic lesion was a rearrangement of the transcription factor *DUX4* occurring in 4% to 5% of childhood cases. At least the *ERG* deletion has been associated with a good prognosis even in cases with codeletion of *IKZF1*. Strong CD371 expression may point to the presence of DUX4 rearrangement.

Alterations in the transcription factor PAX5 contribute to the pathogenesis of BCP-ALL as initiating events (PAX5 P80R, rearrangements/focal intragenic amplifications in PAX5-altered ALL [PAX5alt]) or cooperating lesions (eg, PAX5 focal deletions in 30% of ETV6-RUNX1 ALL, and PAX5 mutations in multiple subtypes). Germline alterations in PAX5 that predispose to ALL have also been identified. The prevalence of PAX5 P80R increases with age and is associated with intermediate to favorable prognosis. An increased frequency of mutations in the Ras and JAK-STAT pathway suggests a potential role for targeted therapies.

The transcription factor ZNF384 can rearrange with a number of partner genes and occurs in 1% to 6% of children and 5% to 15% of adult B-lineage ALL. These cases have a characteristic low CD10 expression and coexpress the myeloid markers CD13 and CD33 and can be found in mixed-phenotype acute leukemia (MPAL). The prognostic significance varies depending on the fusion partner.

Finally, *MEF2D* rearrangements, which occur in 1% to 4% of pediatric and 7% of adult ALL cases, have either a unique expression pattern or cluster with the *BCR-ABL1*-like cases when the partner gene is *CSF1R*. *MEF2D* rearrangement is a marker for worse than average prognosis in a compiled heterogeneous population.

Copy number alterations: important secondary lesions

Several genes of importance for leukemogenesis, such as *IKZF1, CDKN2A, RB, BTG1,* and *PAR1*, frequently have copy number alterations in ALL. Most of these cases are interpreted as deletion of a tumor suppressor gene. These alterations do not seem to represent primary events in most cases because they occur across the canonical groups, frequently in subclones, and are inconsistently represented at relapse. Early reports suggested a simple association with poor outcome, but more recent data indicate that a poor outcome applies only to patients with either a slow treatment response or when the *IKZF1* mutation is associated with additional recurrent copy number alterations and not in combination with the favorable changes (*ETV6-RUNX1*/high hyperdiploidy).

Genetic changes associated with T-cell ALL

Transcription factors

Subgroups of T-cell ALL (T-ALL) are characterized by the presence of specific leukemia-initiating chromosomal rearrangements and mutations that aberrations leading to aberrant expression of transcription factors and oncogenes, such as homeobox genes (*TLX1* [*HOX11*], *TLX3*

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[*HOX11L2*], *NKX2.1*, *NKX2.2*, *NKX2.5, HOXA*), LMO genes (*LMO1, LMO2*), basic helix-loop-helix factors (TAL1, TLX1, TLX3), or others. Such aberrations can be caused by chromosomal translocations involving one of the T-cell receptor (TCR) genes, chromosomal rearrangements with other regulatory sequences, duplication/amplification of transcription factors, and mutations or small insertions generating novel regulatory sequences acting as transcription enhancers. Genomic sequencing approaches have identified >100 genes that can be mutated in T-ALL. Notably, the majority of genetic alterations that have been identified do not independently predict T-ALL outcome, which is most strongly predicted by assessment of MRD, with few exceptions that are listed in the following.

Nonfusion somatic mutations and copy number alterations

Notch

Constitutive activation of Notch signaling, which has important roles in hematopoiesis, angiogenesis, cell proliferation, apoptosis, and T-cell development, is a secondary genetic event and the most common abnormality in T-ALL, found in approximately 70% of cases. Mechanisms of Notch activated include mutations in *NOTCH1*, *FBXW7* (15%), or rarely chromosomal translocation t(7;9)(q34;q34.3), which juxtaposes *NOTCH1* and *TCRB*. *NOTCH1* or *FBXW7* mutations have been associated with a favorable prognosis in adult and childhood ALL. Notch signaling can also be activated secondary to alterations in other signaling pathways, including PI3K/Akt/mTOR and c-myc. This has prompted clinical studies with NOTCH inhibitors, mostly of the γ secretase class of drugs.

Signal pathway deregulation

Numerous lesions induce dysregulation of signaling pathways such as JAK-STAT (IL7R, JAK1, JAK3, and DNM2), Ras (NRAS, KRAS, and NF1), PI3K-AKT (PTEN, AKT1, PIK3CA, and PIK3CD), and of translation regulators (CNOT3, RPL5, and RPL10), Some of these aberrations may lend themselves to targeted therapeutic intervention.

Epigenetic changes

Recent genomic studies have identified recurrent lesions in genes involved in DNA methylation (*DNMT3A, DNMT3B, TET1, IDH1, IDH2*), histone methylation (*EZH2, SUZ12, MLL1, MLL2, DOT1L, SETD2, EED, JARID2, UTX, JMJD3, NSD2*), and histone acetylation (*CREBBP, EP300, HDAC7, HDAC5, NCOA3*) in T-ALL. There is an indication that epigenetic changes may correlate with poor outcome and chemoresistance. None of the other aberrations has been shown to predict outcome consistently and independently from end-of-consolidation MRD.

Subgroups defined by gene expression signatures and kinase activation

BCR-ABL1–like ALL

A unique subgroup referred to as either Philadelphia-like or BCR-ABL1–like ALL was first identified in pediatric patients based on gene expression signatures resembling those observed in Ph^+ ALL, but in the absence of the BCR-ABL1 translocation. It is found at varying frequencies in all age groups, ranging from 10%-15% in children up to nearly 30% in young adults, and is considered to contribute to the inferior outcome of adolescent and young adult (AYA) patients compared with children. BCR-ABL1-like ALL belongs to a group of so-called "B-other" ALL and is exclusive to patients lacking KMT2A rearrangements, TCF3/PBX1 and BCR-ABL1. Diagnosis is challenging because the group is genetically very heterogeneous, encompassing multiple rearrangements that affect >15 kinase or cytokine receptor genes, most fusions involving ABL-class genes (ABL1, ABL2, CSF1R, LYN, PDGFRA, PDGFRB); (ABL1, ABL2, PDGFRA, PDGFRB, CSF1R, and LYN), alterations driving JAK-STAT signaling (eg, rearrangements and mutations/deletions of CRLF2, JAK2, EPOR, TYK2, IL7R, SH2B3, JAK1, JAK3, TYK2, IL2RB), mutations activating Ras signaling (NRAS, KRAS, PTPN11, and less frequently others [FLT3, FGFR1, NTRK3]). Compared with other BCP-ALL, BCR/ABL1–like ALL displays a higher incidence of IKAROS family zinc finger 1 (IKZF1), early B-cell factor-1 (EBF1), paired box gene 5 (PAX5), and V-set pre–B cell surrogate light chain 1 (VPREB1) deletions. Cytokine receptor–like factor 2 (CRLF2) rearrangements/overexpression are present in nearly half of BCR-ABL1-like ALL in AYAs and adults. Unfortunately, there are no universally agreed diagnostic criteria for this subgroup. Different gene panels used for the early hierarchical clustering and prediction analysis of microarray classifier showed little overlap and the 2 methods showed incomplete concordance in assigning patients to the BCR-ABL1-like subgroup. Several groups have devised their own simplified algorithms to identify BCR-ABL1–like ALL based on 9-15 gene panels assessed either by low-density array or quantitative real-time polymerase chain reaction (qRT-PCR), or by combining quantification of gene expression with other techniques including flow cytometry for CRLF2 expression, FISH analysis for JAK2 and other gene mutations and WES, WGS and RNA-seq. Even though the provisional

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entity of "B-ALL with translocations involving tyrosine kinases or cytokine receptors (*BCR/ABL1*–like ALL)" has been added to the 2016 World Health Organization classification of myeloid neoplasms and acute leukemias, there are as of yet no commonly accepted diagnostic criteria. Availability of standardized criteria and assays are highly desirable as the diagnosis of BCR-ABL1–like ALL does not have only prognostic implications but also indicates the presence of therapeutic targets, many of which can be actioned by available kinase inhibitors. The clinical features and therapeutic implications of BCR-ABL1–like ALL are discussed later in this chapter.

Early T-progenitor ALL

ETP-ALL is an uncommon subgroup (5%-36%) of T-ALL that was included as a provisional entity in the 2016 update to the WHO classification of acute leukemia and is characterized by unique immunophenotypic and genetic features. Limited data point towards a higher prevalence in adults compared with the pediatric population but literature, especially for adults, is limited. ETP-ALL displays genetic and transcriptional features similar to a hematopoietic stem cell and resembles immature, lineage ambiguous leukemias that are variably classified by immunophenotype, occasionally making it challenging to distinguish from MPAL/ acute leukemias of ambiguous lineage [ALAL]). The immunophenotype of ETP-ALL resembles that of earliest stages of T-cell development (cytoplasmic $CD3^+$, $CD7^+$; $CD8^-$, $CD1a^-$, CD5 weak and positive for 1 or more stem cell or myeloid antigens, such as CD34, CD117, CD13, CD11b, HLADR, and CD65).

At the molecular level, a majority of patients harbor mutations, which are clustered in the RAS signalling pathway, involve cytokine receptors or affect genes involved in histone modifications. Genetic changes resulting in increased interleukin 7 (IL7) signaling attracted particular attention because of its role in normal T-cell development. The interaction of IL7 with the heterodimeric IL7 receptor induces Janus kinase 1 (JAK1) and JAK3 phosphorylation and subsequent recruitment and activation of signal transducer and activator of transcription factor 5 (STAT5). Activating mutations in *IL7R*, *JAK1*, *JAK3,* and/or *STAT5* are present in 20%-30% of T-ALL cases, with a higher representation within the TLX3-positive, HOXA-positive, and ETP-ALL patient subgroups.

Notably, the IL7R signaling cascade can be hyperactivated in patients that do not carry genetic aberrations in the IL7R, JAK, or STAT5 genes, indicating that additional mechanisms exist to activate this pathway.

The PI3K/Akt/mTOR pathway is also frequently activated in T-ALL, most often caused by inactivation of PTEN.but also by mutations in *AKT1, PI3KCA, PI3KR1*, and *IL7R*.

The importance of host germline genomics

Susceptibility to ALL

There are a number of genetic syndromes with a clearly increased risk of ALL, the most common of which is Down syndrome (DS) (discussed separately under treatment). Other susceptibility syndromes include defects in DNA repair, such as ataxia telangiectasia, Bloom syndrome, and others. Because these syndromes also affect the impact of therapy on the host, they are important to diagnose. This is also true for Li-Fraumeni syndrome, which has rather recently been associated with hypodiploid ALL (91%) as described.

The early onset of many ALL and detection of some initiating somatic genomic abnormalities at birth suggest there may be an inherited genetic basis for susceptibility even in the absence of distinct genetic syndromes. More detailed and extensive genetic testing, particularly in familial cases and in patients with unknown genetic conditions, has also revealed new germline variants in several genes associated with somatic changes in leukemic cells. Genome-wide association studies (GWASs) have identified >12 susceptibility regions for ALL regions harboring risk variants, including *IKZF1*, *CDKN2A/B*, *GATA3*, *CEBPE*, *ERG,* and others. A recent analysis of common subtypes of BCP-ALL defined by somatic genetic lesions have identified subtype-specific GWAS associations for high-hyperdiploid ALL (10q21.2; *ARID5B*), *ETV6-RUNX1* fusion–positive ALL (2q22.3) and Philadelphia chromosome-like ALL (10p14; *GATA3*). It is hoped that genes elucidated from GWAS functional annotation may represent promising therapeutic targets for drug discovery.

Host genome and adverse effects of treatment

Host-genome variants that increase the likelihood of side effects to therapy have also been described affecting for instance the incidence of bone osteonecrosis due to corticosteroid therapy and to pancreatitis as a result of asparaginase therapy. These genetic variants do not yet influence the routine choice of therapy, but therapy is influenced by differences in nucleoside metabolism:

- Genetic variants affect the metabolism of thiopurines. One in 300 have an inherited homozygous deficiency of thiopurine *S*-methyltransferase (TPMT), the enzyme that catalyzes the *S*-methylation of mercaptopurine. Mercaptopurine should be reduced markedly (eg, 10-fold reduction) in these patients to avoid potentially fatal hematologic toxicity. Previously, both

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a better antileukemic effect and an increased risk of second malignancy were described in patients heterozygous for the *TPMT*-gene variant, but more recent reports have negated these initial findings; therapy should largely be titrated as for wild-type patients.

- Severe myelotoxicity has been observed in patients of Asian and Hispanic ancestry with a homozygous variant of the nucleoside diphosphate-linked moiety X-type motif 15 (*NUDT15*) gene. Heterozygous effects of the *NUDT15* polymorphisms have not been extensively studied.

The Clinical Pharmacogenetics Implementation Consortium has developed guidelines for thiopurine therapy (updates at http://www.pharmgkb.org) based on the association between clinical effects and phenotype or genotype of the thiopurine methyltransferase. Guidelines have recently also been updated with some NUDT15 data.

Prognostic factors: overview

Because ALL is universally fatal if untreated, it is only meaningful to discuss prognostic factors when curative therapy is administered. Such therapy has varied in intensity and has had very different cure rates over time, which means that most risk factors are valid only in the context of a particular therapy. Many early clinical prognostic factors, identified when ALL patients were first cured with considerably less intensive therapy, have lost their independent prognostic significance as more intensive therapies have been introduced. The discovery of genetic subgroups has further refined the stratification systems; however, the genetic subgrouping has seen the same development over time, with generally decreasing impact when risk-adapted therapy has been implemented. Because of the impact of therapy and the large number of prognostic factors, current protocols integrate individualized algorithms for stratification.

Table 20-3 lists some prognostic factors that may be used for risk stratification and/or risk-adapted therapies in current clinical protocols.

Leukocyte count and age

Leukocyte count is a continuous variable, with increasing counts at diagnosis conferring a poorer outcome in B-lineage ALL. In childhood ALL, there is general agreement, as supported by NCI guidelines, to use a presenting age between 1 and 9 years and a leukocyte count of $<50 \times 10^9$/L as minimal criteria for low-risk B-lymphoblastic ALL. Infants have an inferior prognosis, likely linked to genotype rather than age, as infants without *KMT2A* rearrangements have only a slightly worse prognosis than older children do. Age and leukocyte count have less prognostic value in T-cell ALL. In adult ALL, age <35 years and a leukocyte count of $<30 \times 10^9$/L are considered favorable prognostic indicators, and a leukocyte count of $>100 \times 10^9$/L is considered a poor prognostic feature for T-cell ALL in some protocols. In adult protocols, outcomes frequently decrease with increasing age.

Sex

Male sex is associated with a higher risk profile in many study populations, but, with risk-adapted therapy, the differences in outcome found in early studies are mostly abrogated. Some protocols still stratify boys to longer maintenance therapy; however, standard practice is moving away from prolonged maintenance in males. Female sex has, in some studies, been associated with a higher risk of treatment-related mortality.

Race

Many population-level studies show differences in outcome between ethnic groups. White people tend to have the best outcome with treatment, but patients of Hispanic, Black, and, in some cases, Asian ancestry have worse outcomes with treatment. In protocol-specific settings, some of these differences are explained by higher-risk characteristics; pharmacogenomic variation and socioeconomic factors have been proposed to contribute by affecting access to care.

Immunophenotype

T-cell ALL has, in large comprehensive protocols, lost most of its prognostic importance as a high-risk factor, but many protocols still include some upgrading of the treatment intensity of T-cell patients. However, several studies have shown that T-cell patients with a good response to initial therapy can be treated according to standard-risk protocols.

CNS involvement

CNS involvement at diagnosis is present in 3%-5% of children (as high as 10% in infants) and in about 5% of adults. CNS involvement (increased cell count of leukemic origin in diagnostic cerebrospinal fluid (CSF)) is associated with an increased risk of relapse, particularly CNS relapse. Most protocols stratify patients with CNS involvement to extraintrathecal therapy and/or CNS irradiation, and some also increase systemic therapy. The prognostic impact of lower grade (leukemic cells, but no increase in cell number) CNS infiltration is less clear, but a recent study indicates that intensified CNS-directed therapy is probably warranted. The introduction of leukemic cells by a so-called "traumatic tap" at diagnostic lumbar puncture

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Table 20-3 Prognostic factors used for risk stratification

Prognostic factors	Favorable	Adverse
Adult		
Age (years)	<35	>60
Leukocyte count (10^9/L)	<30 for B cell	>100 for T cell
Immunophenotype	Thymic T-ALL	Early T-cell precursor (in some studies)
Genotype	High hyperdiploid (in some studies)	*BCR-ABL1; MLL* rearrangement
		Hypodiploidy <44
Minimal residual disease after induction	Low/absent	High
Pediatric		
Age (years)	1-9	<1 or >10
Leukocyte count (10^9/L)	<50	>50
Immunophenotype	B-lymphoblastic	T cell (ETP-ALL)
Genotype	Hyperdiploidy >50; *ETV6-RUNX1*	Hypodiploidy <40; *KMT2A* rearrangements, *iAMP21, IKZF1* deletions or mutations
Minimal residual disease after induction	<0.1%/<0.01%/negative	>0.01%-0.1% (59%; 5-year EFS) >0.1%-1% (49%; 5-year EFS) >1% (30%; 5-year EFS)
Minimal residual disease after consolidation	Negative (T cell)	Positive (T cell)

(LP) (definitions include CSF with >100 red blood cells or ≥10 red blood cells/μL CSF) is associated with an inferior outcome and, in most contemporary protocols, CNS-directed therapy is intensified.

Secondary acute lymphoblastic leukemia

Secondary ALL (sALL) following treatment for a primary malignancy is rare compared with secondary myeloid diseases. Data on cytogenetic and molecular characteristics of sALL are limited, with 11q23 abnormalities, mainly t(4;11)(q21;q23) as the most frequent genetic findings. Other translocations included t(9;22)(q34;q11) and t(8;14)(q24;q32). An analysis of the Surveillance, Epidemiology, and End Results (SEER) database, evaluating patients with sALL after various cancers or lymphoma with a latency period of at least 12 months, identified 4124 cases of de novo ALL and 79 cases of sALL. At diagnosis, patients with sALL were significantly older than patients with de novo ALL. While multivariate analysis suggested that sALL is an independent predictor of poor outcome, median survival in both groups was conspicuously low, casting doubt on the generalizability of these findings.

Minimal/measurable residual disease

MRD: principles

While MRD has been assessed in ALL for >30 years, with increasing sensitivity, MRD has taken center stage as the most important independent prognostic parameter and increasingly is replacing morphology for evaluating response, defining treatment failure, or identifying disease recurrence. Nevertheless, it is important to recognize that clinical interpretation of the results of MRD analysis critically require knowledge of the clinical context and technical considerations concerning type of methodology, source and quality of material, timepoint of analysis, and terminology with respect to specific MRD thresholds.

Minimal residual disease is most frequently surveyed using highly sensitive multiparametric flow cytometry (MFC) or molecular analysis of clone-specific immunoglobulin/T-cell receptor [*IG/TR*] gene rearrangements or molecular markers such as fusion gene transcripts. The value of MRD as the strongest prognostic factor independent of traditional pretherapeutic risk factors has been shown in both children and adults with ALL and has reduced reliance on of clinical and genetic factors as predictors of outcome.

Flow cytometry MRD

Multiparametric flow cytometry for MRD analysis is based either on the discrimination of ALL cells from normal counterparts or, more precisely, on the identification of the leukemia-associated aberrant immunophenotype. The leukemia-associated aberrant immunophenotype can be identified in >90% of patients with ALL, and its detection is relatively easy and fast, although the maximum sensitivity of MFC MRD detection is approximately 1 log

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lower than that of molecular methods. It is important to recharacterize leukemia at times of relapse as predominant clones may evolve that display downregulation of canonical B-cell markers, particularly following therapy targeting surface antigens.

Molecular MRD

Detection of leukemia-specific rearrangements of immunoglobulin and T-cell receptor (*IG/TR*) genes by qRT-PCR is possible in >95% of patients with ALL. Sensitivity is determined separately for each assay and routinely reaches 10^{-4} to 10^{-5} (1 leukemic cell in 10,000-100,000 normal cells). Initial target identification is laborious, time-consuming, and expensive, but it has been optimized and standardized through the efforts of the EuroMRD Consortium (http://www.euromrd.org), which now includes nearly 60 laboratories worldwide.

Target identification and quantitative MRD-monitoring may be facilitated by NGS techniques, which can reach a sensitivity at least comparable to PCR and may in addition detect emerging subclones. NGS testing, with United States Food and Drug Administration (FDA) approval of Adaptive Biotechnologies' ClonoSEQ assay for use in B-ALL, is starting to be increasingly integrated into clinical practice.

Specific genetic aberrations applicable to MRD detection are present in about 30% to 40% of BCP-ALL and 10% to 20% of T-ALL. Both *KMT2A* rearrangements and Ph^+ ALL may routinely be monitored by qRT-PCR. The approach is easier and less expensive than *IG/TR* rearrangement detection but interpreting RNA-based results is more challenging than interpreting DNA-based results and simultaneous testing may deliver discordant results.

MRD in clinical management

Stratification

MRD is universally accepted as stratification criterium for adult and pediatric patients, both with and without HSCT, but informative thresholds differ depending on the time points, analytical techniques, and therapeutic context .In general, end-induction MRD levels <0.01% are considered an excellent response, whereas end-induction MRD ≥0.01% constitutes a poor response.

Patients in morphologic CR with high persistent MRD levels after of the first consolidation block should be considered for allohematopoietic stem cell transplantation (allo-HSCT). Study data from the German Multicenter Study Group for Adult ALL (GMALL) demonstrated significantly higher probability of continuous CR in patients with molecular failure who underwent SCT in first complete remission (CR1) (66% versus 11%). The GMALL also showed that MRD levels $<10^{-4}$ after soon after induction were predictive of very good outcome, whereas persistent MRD after consolidation (weeks 12 and 16) was more informative in terms of inferior outcome and constituted an indication for HSCT. The predictive role of pretransplanation MRD is more controversial: whereas higher levels of MRD retain their negative predictive power even after allogeneic SCT in some studies, SCT was shown to eliminate the unfavorable impact of a poor MRD response in the French GRAALL-2003 and -2005 trials. In contrast, SCT did not improve outcome in MRD good responders. Detection of MRD after SCT is associated with a high cumulative incidence of relapse and warrants intervention.

MRD integrated with genetic subtype

Several studies have demonstrated that considering MRD levels in the context of specific genetic subtypes allows more refined risk-group stratification.

In a recent analysis of 3113 patients who were treated in the UKALL2003 study, MRD was considered as a continuous rather than dichotomized variable, and analyzed separately in in groups of patients who were defined by clinical features and sentinel genetic lesions. While the risk of relapse was correlated with MRD level within each genetic risk group, the absolute relapse rate associated with a specific MRD value differed significantly by genetic subtype.

This approach of integrating continuous MRD values with multiple risk factors led to the development of a novel prognostic index that was validated in large pediatric patient cohorts (UKALL2003, COALL-03, DCOG-ALL10, and NOPHO-ALL2008 trials). This model based on white cell count at diagnosis, pretreatment cytogenetics, and end-of-induction minimal residual disease was a superior predictor of relapse than established algorithms.

In a related approach by the French Acute Lymphoblastic Leukemia Study Group (FRALLE), MRD combined with *NOTCH1, FBXW7, RAS, and PTEN* mutational status and white blood cell count improved outcome prediction in pediatric T-cell acute lymphoblastic leukemia.

Summary

MRD has become the most important parameter to assess the depth of the initial response to treatment, for risk stratification monitoring of disease burden during treatment, and is increasingly accepted as an end point in clinical trials. The increasing relevance of MRD for clinical management decisions is highlighted by the FDA and

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EMA approvals of the bispecific T cell–engaging antibody blinatumomab (discussed later in more detail) for MRD-positive ALL, and use of postconsolidation MRD as an eligibility criterium for a study of CD19-specific CAR T cells (tisagenlecleucel) in patients with high-risk B-ALL (Cassiopeia, NCT03876769)

Correct interpretation of MRD data depends on recognition of the unique strengths and weaknesses of the individual methods, and that their sensitivity and specificity may vary across treatment time points and therapeutic settings. Bone marrow assessments remain crucial in BCP-ALL, as MRD levels are typically 1-3 logs lower in peripheral blood than in bone marrow, a finding distinct from T-ALL. Because of the variable limits of detection between different assays and differences in clinical implications of different thresholds, the term "measurable residual disease" instead of "minimal residual disease" may be more appropriate.

Treatment of ALL

General principles

In children and adults with ALL, chemotherapy has been the mainstay of treatment and remains central to upfront treatment of most patients with ALL, with exception of Ph^+ ALL, which has seen a paradigm shift towards use of targeted agents. Following a rapid diagnostic workup which in adults and European-based pediatric trials is conducted parallel to a short corticosteroid-based cytoreductive treatment (prephase), the typical therapeutic approach is to initiate treatment with a course of induction chemotherapy encompassing several cytotoxic drugs with different mechanisms of action. The duration of this induction phase ranges from 3 to 6 weeks depending on the regimen and protocol used. Following induction, a disease assessment is performed which further informs risk stratification. Patients with detectable disease following induction using morphologic criteria are at high-risk of remaining nonresponders or eventually experiencing relapse and are therefore considered for treatment intensification or alternative treatments. More sensitive measures of MRD now routinely complement and increasingly replace traditional cytologic analysis for stratification into risk groups that determine whether and how the initial therapeutic approach will be modified.

In patients achieving a complete hematologic remission/complete remission (CHR or CR), continuation of cytotoxic therapy is imperative to prevent disease recurrence, with most protocols mandating at least 2 years of chemotherapy involving multiple agents unless a patient undergoes stem cell transplantation. This postremission treatment is subdivided into a period of consolidation therapy consisting of repeated cycles of intensive chemotherapy of about 6 months total duration, followed by obligatory maintenance therapy which is less intensive but prolonged. As the minimum duration of maintenance needed to be curative remains uncertain, a total of 2 years following achievement of complete remission is customary in pediatric and adult patients. Even more prolonged (up to 3 year) maintenance previously used in boys is becoming obsolete. These principles do not apply to patients undergoing HSCT in CR1, which when indicated is usually scheduled as early postremission therapy. While HSCT retains a more central role in treatment algorithms for adult than for pediatric patients, ongoing reassessment, and refinements in the indication for HSCT have prompted us to address this topic in a joint paragraph.

For historical reasons, differences in disease biology and remaining differences in outcome between children and adults with ALL, despite progressively enhanced survival over the last 5 decades, we discuss the principles of induction, consolidation, and maintenance chemotherapy separately for patients in different age groups. Specifically, we address treatment for:

- Children and adolescents
- Fit adults
- Older and frail persons

Across all cohorts, the CNS space is a well-recognized sanctuary site for leukemia and CNS-directed treatment. CNS prophylaxis is a critical element to successful ALL therapy. The underlying principles and practice of administering CNS prophylaxis and treating active CNS (usually meningeal) leukemia have converged for children and adults and will therefore be covered independently of patient age.

Major advances in treatment of relapsed ALL in children and adults have been brought about by recent developments in immunotherapy, most notably antibody-drug conjugates, the bispecific T-cell engager (BiTE) blinatumomab and chimeric antigen receptor T cells.

Treatment of B-precursor ALL and T-ALL in children and adolescents

Usually, childhood ALL cases are divided into low- (standard) risk, high- (intermediate or average) risk, and very-high-risk groups, although the US Children's Oncology Group advocates 4 categories, including a very-low-risk group. Upon stratification, in the United State, risk groups tend to be sequestered into separate trials. In Europe,

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comprehensive treatment protocols, spanning diagnosis, stratification, and therapy, is often implemented. Infants are often treated with distinct regimens as are children with Ph^+ ALL.

While risk-directed therapy is the fundamental principle underlying therapy for childhood ALL, risk stratification lacks consensus and varies across protocols. Additionally, some prognostic factors such as cytogenetics and MRD response to induction are not available at time of diagnosis. As a consequence, current protocols include individualized stratification systems in which the final risk groups may evolve during therapy, based on biology and response to therapy.

Children and adolescents: remission induction

Rates of CR following induction range from 97% to 99% with contemporary chemotherapy. The induction regimen usually contains 3 or 4 drugs, typically a glucocorticoid (prednisone, prednisolone, or dexamethasone), vincristine, and asparaginase with or without an anthracycline. Cyclophosphamide may be added for higher-risk patients. The intensive chemotherapy is, in some European protocols, preceded by a prephase of a single corticosteroid to reduce the leukemic cell burden. The response to this prephase has been used for stratification in European but not US studies. Although prednisone and dexamethasone both yield comparable results when given in equivalent doses, dexamethasone still appears to yield improved CNS control and is used preferentially in postremission therapy in current clinical trials. At higher doses (10 mg/m^2/day) in induction, in some studies, dexamethasone dose intensification associates with increase in deaths and worse outcome after relapse, thereby offsetting benefit of reduced relapse rate. CNS-directed therapy is started early, and frequency depends on the presenting CNS status, the patient's risk of relapse and the intensity of the primary systemic treatment. This topic is described in detail in the following section addressing CNS prophylaxis and management of CNS leukemia.

Of the various anthracyclines given to patients with ALL, none has proved superior to any other; however, daunorubicin is used most commonly.

L-Asparaginase is the only ALL-specific chemotherapy drug which acts by depleting the serum asparagine levels. The pharmacodynamics of asparaginase differ by formulation, and, in terms of leukemic control, the dose intensity and duration of asparaginase treatment (ie, the amount of asparagine depletion) are far more important than the type of asparaginase used. Because of the lower immunogenicity, less frequent dosing because of significantly longer asparagine depletion time, and feasibility in intravenous administration of PEG-asparaginase (a polyethylene glycol form of the *Escherichia coli* asparaginase) compared with the native product, PEG-asparaginase has replaced native *E coli* asparaginase as the first-line treatment in most protocols, but availability of the pegylated product is a limiting factor in some countries.

Immunoreactivity against asparaginase is a significant problem and may cause allergic reactions as well as silent inactivation of the drug. Most major allergic reactions to both native and pegylated asparaginase seem to be associated with inactivation, but not all antibody formation causes inactivation of asparaginase activity, and allergy-like reactions are sometimes not associated with inactivation. For this reason, all patients with significant suspected allergic reactions should be tested for asparaginase activity after the offending dose. If no activity is detected, patients should be treated with the alternative product derived from *Erwinia chrysanthemi*. It is a clinical decision whether to continue with the pegylated product after premedication with antihistamine and steroids if activity is still adequate. Standard monitoring of asparaginase activity with subsequent possibility of dose adjustment has been shown to be of benefit in some protocols, and further trials are ongoing, both to avoid overtreatment and to detect silent inactivation, which should also indicate a change in product used.

Children and adolescents: postinduction/postremission

At the end of induction, most protocols have a point of response evaluation and stratification. In some protocols, risk-adapted therapy diverges, whereas some protocols have a common start of postinduction therapy to allow for MRD evaluation. Although there is no dispute about the importance of this treatment, there is no consensus on the best regimen and duration of treatment. Many protocols continue with a therapy element developed by the Berlin-Frankfurt-Münster consortium (BFM-IB protocol) with cyclophosphamide, 6-mercaptopurine, and repeated 4-day blocks of injections of cytarabine, whereas other regimens include high-dose methotrexate (HDM) with mercaptopurine or regimens based on a lower dose of methotrexate. Patients with a poor response to therapy are, in some protocols, shifted to more intensive, block-based therapy. Delayed intensification (or reinduction), also first introduced by the BFM, is a widely used approach consisting of a repetition of therapy similar to the first remission induction therapy approximately 3 months after the end of remission induction. Delayed intensification has been repeated (double-delayed intensification) in studies with somewhat conflicting results, probably reflecting

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the treatment stratification and the context of the therapy. Extended asparaginase therapy, starting during induction or early postinduction therapy, has received increasing attention and is under study in a randomized fashion in several protocols. Early results from one such study fail to repeat the benefit of prolonged continuous asparaginase exposure from previous trials, indicating that this benefit may be context dependent.

T-ALL/LL specific: Based on the COGAALL0434 Phase III study investigating the role of nelarabine in intermediate and high-risk patients with T-ALL/LL, Nelarabine is now incorporated onto a BFM backbone for intermediate and high-risk T-ALL/LL patients. Nelarabine is a nucleoside prodrug that terminates DNA replication. The phase III study was double randomized to distinctly compare high-dose methotrexate (HD MTX) to escalating low doses of methotrexate (Capizzi MTX, which includes PEG-asparaginase) and addition of nelarabine compared to treatment without nelarabine. Nelarabine randomization was postinduction and six 5-day courses were given (2 in consolidation, 1 in delayed intensification, 3 in 3 first cycles of maintenance). Outcomes demonstrated a 5-year disease-free survival of 88% in the nelarabine arm as compared to 82% in the nonnelarabine arm, with fewer CNS relapses described in the nelarabine arm. Interestingly, the Capizzi MTX arm associated with improved outcomes as compared to HD MTX and the arm with optimized 5-year disease-free survival of 91% was the nelarabine and Capizzi MTX arm. Based on these data, nelarabine is now incorporated into trials for intermediate and high-risk T-ALL/LL.

Children and adolescents: maintenance (continuation) therapy

The rationale behind the use of maintenance treatment is the elimination of slowly growing subclones that persist after induction and consolidation treatments by prolonged exposure to antimetabolite drugs. A combination of methotrexate administered weekly and 6-mercaptopurine (6MP) administered daily constitutes the standard continuation regimen for ALL. In the United States, monthly 5-day steroid pulses and monthly vincristine doses have traditionally been included in continuation therapy. There is a movement towards decreasing the vincristine frequency and shortening duration of use. Current protocols are decreasing vincristine dosing frequency to every 3 months, specifically for lower-risk patients, and protocols are actively studying shortened duration of vincristine during continuation in a randomized manner. In some protocols, boys have been treated with a longer duration of continuation therapy than girls because, as male sex has historically been associated with a poorer prognosis. With improved outcome, both boys and girls are now treated with the same duration of 2 to 2.5 years of continuation therapy in most clinical trials. The administration of methotrexate and mercaptopurine, titrated to preset limits of tolerance (as indicated by a range of leukocyte count depression), has been associated with improved clinical outcome. Many investigators advocate that the drug dosage be adjusted to maintain leukocyte counts $<3 \times 10^9$/L and neutrophil counts between 0.5×10^9/L and 1.5×10^9/L to ensure adequate dose intensity, yet not induce excessive myelosuppression. Overzealous use of mercaptopurine is counterproductive, however, resulting in interruption of chemotherapy because of neutropenia and reduction of overall dose intensity. Furthermore, longer duration of the maintenance phase has been associated with the development of secondary myelodysplastic syndrome and acute myeloid leukemia (AML), which additionally limits dosing.

Mercaptopurine should be taken daily at a fixed timepoint to facilitate compliance, and in contrast to older recommendations concurrent milk, milk products, or other foods do not need to be avoided to preserve chemotherapy effect. Although oral methotrexate is standard, parenteral administration may overcome concerns about bioavailability or treatment adherence, especially in adolescents. Antimetabolite treatment should not be withheld because of isolated increases of liver enzymes; such liver toxicity is tolerable and reversible. In event of severe toxicities or challenges achieving targeted neutrophil count, consider pharmacogenomics and possibility of noncompliance (evaluate metabolites).

Intermittent pulses of vincristine and a glucocorticoid have been adopted widely in continuation regimens for childhood ALL, although its impact on outcome in contemporary regimens featuring early intensification is still unclear.

Special subgroups of ALL in children

Down syndrome

Patients with DS have a 10- to 20-fold higher relative risk for leukemia, and they constitute ~2% of pediatric ALL patients. These patients have the same age range as the general pediatric population, with the exception of a lack of cases in the infant age group. ALL patients with DS have a much lower incidence of T-cell and mature B-cell ALL and have a low frequency of other specific genetic subtypes of precursor B-cell ALL, but they have a high frequency of activating somatic *JAK2* mutations, affecting approximately 20% of the cases. A compilation of data from several study groups showed that as many as 69% of DS cases

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have *CRLF2* rearrangements, some of which co-occurred (about 21% of all cases) with activating *JAK2* mutations. Although the outcome has improved with modern treatment, these patients still fared significantly worse than other children with ALL, likely because of a combination of reduced tolerance to chemotherapy, such as dexamethasone and methotrexate, resulting in reduced compliance to protocol treatment, but also to excessive treatment-related deaths. Another possible contributing factor is the paucity of genetic changes associated with better prognosis in this patient population. The *JAK2/CRLF2* alterations themselves do not seem to confer an adverse prognosis compared with other children with DS. However, in a recent Dutch/UK study, *IKZF1* deletions were found in 35% of all patients, and patients with such deletions had a very high risk of relapse, with an event-free survival of only 21% to 45% in the different national cohorts studied. It is important that although biologically distinct, patients with Down syndrome are included on clinical trials as to continue to improve outcomes in this population.

Infant ALL

Infant ALL accounts for 2%-3% of childhood ALL and is characterized by a high frequency of 11q23 chromosomal abnormalities and rearrangements of the *KMT2A* gene (70%-80%), a CD10-negative pro-B immunophenotype, a tendency towards hyperleukocytosis, CNS involvement, and an inferior outcome. Large collaborative studies including agents such as vorinostat and bortezomib are necessary to study this rare subset of patients, but despite very large consortium efforts, progress has been modest at best over the last 15 years, with overall survival hovering between 50% and 60%. An ongoing clinical trial is testing the safety and efficacy of bortezomib and vorinostat in combination with chemotherapy commonly used to treat ALL in infants (NCT02553460). Bortezomib and vorinostat have been approved by the FDA to treat other cancers in adults, but they have not been approved for treating children with leukemia.

Application of pediatric treatment principles to adult ALL

Recognition that the improved survival in childhood ALL over the past 5 decades was attributable to treatment intensity prompted studies applying pediatric-like intensive regimens to AYA up to about 40 years. Treatment follows the same sequence of induction, consolidation and maintenance but intensifies the use of nonmyelosuppressive corticosteroids (CS), vincristine, asparaginase, with augmented CNS prophylaxis by more frequent intrathecal applications and the higher activity of systemic CNS-active drugs. Higher cumulative doses of antimetabolites and reduced use of anthracyclines are additional features of pediatric protocols that were addressed in some studies. Numerous prospective European and American studies consistently demonstrated superiority of regimens modelled after pediatric protocols. The Spanish PETHEMA group demonstrated 6-year EFS and OS rates of 63% for young adults aged 19-30 years, while a similar French trial for patients with BCP- and T-ALL aged 15-45 years achieved 42-month EFS and OS rates of 55% and 60%, respectively. In the UKALL-2003 trial, the 16- to 24-year-olds had a 5-year EFS of 71% and OS of 72%, similar to the outcome for patients in the 18-to-45-year-old age bracket treated according to the NOPHO ALL-2008 protocol with 5-year EFS of 74% and OS of 78%. At present, there is no convincing evidence that the Hyper-CVAD protocol provides benefits over the modern BFM-type pediatric regimens in the AYA patient population. By contrast, driven by retrospective data demonstrating superior outcomes in AYA patients treated according to pediatric regimens at pediatric hospitals, a prospective study, CALGB 10403, was launched using identical pediatric doses and dosing schedules to the Children's Oncology Group COGAALL0232 trial, with therapy delivered by adult oncologists in adult treatment centers. This landmark study across patients aged 17-39 demonstrated safety of pediatric therapy with a low treatment mortality of 3% and importantly demonstrated an impressive median EFS of 78 months, as compared to historic control median EFS of 30 months. Three-year OS was 73%, and CALGB10403 and the overall practice to treat AYA patients aligned with pediatric protocols has since been considered the new standard for treating AYA patients.

The upper age limit for adult patients enrolled in studies investigating pediatric-inspired regimens has been variable. Typically, patients beyond the AYA age bracket demonstrated significantly inferior overall and disease-free survival, showing that age retains its importance as a poor prognostic factor of outcome in ALL patients receiving pediatric-inspired therapy, primarily due to greater toxicity. In particular, asparaginase, intensive glucocorticoid and vincristine dosing is more poorly tolerated in adults. Age as a prognostic factor is confounded by a higher proportion of unfavorable genetic subtypes, comorbidities and psychosocial issues affecting treatment compliance.

Fit adults: treatment of B-precursor ALL and T-ALL

Historically, essentially all successful treatment regimens for adult ALL were based on pediatric protocols. The "novelty" of applying modern pediatric regimens to adult patients thus relates more to dose intensity than underlying

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principles or structure of the regimens. The most widely used are the Berlin-Frankfurt-Münster (BFM-type) therapy initially developed by the pediatric BFM Consortium and the hyperfractionated cyclophosphamide, vincristine, doxorubicin (Adriamycin), and dexamethasone (Hyper-CVAD) regimen alternating with high-dose methotrexate and HD cytarabine pioneered by the MD Anderson Cancer Center and patterned after an older pediatric regimen by adding the VAD combination. BFM-style therapy in adults generally follows the same basic strategy of multiagent induction, consolidation-intensification, CNS prophylaxis, and maintenance therapy as in children, although the relative contribution of each of these phases toward disease curability has not been determined rigorously in adult ALL. CNS-directed prophylactic therapy is a critical element of all ALL regimens, as described later in this chapter.

In the past treatment of adults gave less specific consideration to biologic risk but the central role of MRD as the most relevant stratification parameter is now accepted for all age groups. In contrast, indications for HSCT diverge considerably between age groups with far greater emphasis on transplant for adults, including reduced intensity conditioning (RIC) regimens for older or unfit patients. Other strategies for overcoming inferior survival rates in adults considered ineligible for modern intensive pediatric-based protocols increasingly focus on use of newer, nonmyelotoxic targeted therapies that may be added to existing therapy or replace treatment elements that are too toxic for a given patient subset.

T-ALL is treated according to the same principles and using the same regimens as BCP-ALL but has so far not benefited from the development of novel antibody- or cell-based immunotherapies now commonly used for B-lineage ALL. In patients with a large mediastinal mass, avoidance of anesthesia and supine positioning is important during diagnostic workup. Additionally, tumor-lysis syndrome resultant from lysis of large tumor burden can develop into an oncologic emergency extremely rapidly following initiation of therapy, even with steroids alone.

ETP-ALL is a distinct subset with a poor prognosis and several potential targeted treatment options and will be described later. The purine nucleoside analog nelarabine is specific for T cells and is approved for relapsed/refractory T-ALL, as the only addition to the therapeutic armamentarium for precursor T-cell ALL in recent years. In the salvage setting CR rates with single-agent nelarabine are in the range of 30%-55% and permit some patients to undergo allogeneic HSCT as the only curative salvage option for adults with T-ALL. This activity provided the rationale for investigating nelarabine as an addition to intensive frontline treatment for pediatric patients with newly diagnosed, high-risk T-ALL, showing good tolerability and EFS significantly higher than in historic controls. Nelarabine has also been shown to add benefit for intermediate- and high-risk patients in a large, randomized study of children and young adults up to the age of 30. In contrast, there is insufficient evidence for a benefit of adding nelarabine to standard chemotherapy in the frontline setting. The UKALL14 trial is investigating the value of nelarabine added to frontline therapy for adult T-ALL but has not yet reported the results.

Induction phase

Overall >85%-90% of fit adult patients achieve remission in current multicenter studies, which frequently build on a backbone of vincristine, a glucocorticoid (prednisone or dexamethasone), asparaginase, and an anthracycline such as daunorubicin. Resistance and induction deaths contribute about equally to treatment failure and no induction regimen is clearly superior to another. Toxicity of the cytotoxic drugs has hampered further dose intensification and it has been difficult to demonstrate further improvements in overall CR rates with the addition of other drugs, such as cyclophosphamide or cytarabine. Dexamethasone is often preferred to prednisone because it penetrates the blood-brain barrier but is associated with severe infections in a dose- and schedule-dependent manner.

Pioneered in the treatment of pediatric ALL, asparaginase contributes to increased response rates and duration of response in adults, although its benefit for adult patients is not supported by randomized studies. A study by the Cancer and Leukemia Group B (CALGB), now known as the Alliance, 9511, with PEG-asparaginase, showed that patients who achieved effective asparagine depletion had a superior outcome compared with patients who did not achieve asparagine depletion. Ongoing trials by the German Multicenter ALL group of PEG-asparaginase suggest a potential survival benefit in older adults with ALL when the drug is administered at only slightly lower doses than have been used by the pediatricians. The toxicities of asparaginase include allergic reactions, pancreatitis, hyperglycemia, hepatotoxicity, and coagulopathy, which are more pronounced in adults than in children and may be further exacerbated by obesity (body mass index >30) and steatosis of the liver detected on ultrasound evaluation.

Efforts to further improve CR rates and achieve a good molecular response or molecular CR has prompted evaluation of rituximab as nonmyelotoxic, lineage-specific treatment. The B-lineage differentiation antigen CD20 is expressed on ALL blasts of approximately 40% of patients

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with B-cell precursor ALL and has been associated with an adverse prognosis. Across several single-arm studies using different chemotherapy regimens (Hyper-CVAD or GMALL-based) and in a recent large, confirmatory phase 3 trial (GRAALL-2005), adding the anti-CD20 monoclonal antibody rituximab to frontline chemotherapy for younger (up to 60 years) patients with BCP-ALL was well tolerated and improved treatment outcomes, despite having no effect on CR rates. EFS in the GRAALL study improved by 13% from 52% to 65% at 2 years. In contrast, an increased rate of infectious events was noted among older patients. Thus, rituximab may now be considered the standard of care for patients <55-60 years of age with CD20-expressing ALL.

Fit adults: consolidation therapy

A relapse rate 50% to 75% in intensively treated adult ALL patients has led to many variations of postremission consolidation treatment that has typically been modeled after pediatric regimens. Traditionally, this includes agents similar to the 4 or 5 drugs used during remission induction, with the addition of antimetabolites, such as methotrexate, mercaptopurine, or thioguanine. Systemic high-dose (HD) therapy reaches sufficient drug levels in sanctuary sites, such as the CNS. Most protocols employ 6 to 8 courses that contain either HD methotrexate or HD cytarabine ± asparaginase. HD cytarabine is usually administered for 4 to 12 doses at 1 to 3 g/m^2 and methotrexate at 1 to 1.5 g/m^2 and as high as 3 g/m^2. Cyclophosphamide, high-dose cytarabine, and etoposide also have been incorporated into many postremission strategies, although it has been difficult to analyze critically the contribution of each drug or schedule to outcome in adult ALL series.

The CALGB compared a more intensive consolidation regimen that included both early and late intensification using 8 drugs with previous CALGB trials in a phase 2 study. The results showed that median remission duration improved to 29 months, whereas median survival extended to 36 months. The Italian GIMEMA group conducted a study that included randomization of 388 patients to postremission intensification followed by maintenance chemotherapy versus early maintenance therapy without intensification.

In summary, all of these regimens result in similar disease free survival (DFS) rates of ~30% to 40% overall in adult patients treated in cooperative group trials. Younger patients with favorable-risk cytogenetics can have DFS rates of ~60%, whereas <10% to 15% of older adults (>60 years) survive long-term. The use of autologous HSCT (auto-HSCT) and allo-HSCT as postremission therapy for ALL will be discussed in a separate section.

Hyper-CVAD as induction and consolidation regimen

An alternative treatment regimen known as Hyper-CVAD was developed at the MD Anderson Cancer Center and uses hyperfractionated cyclophosphamide, dexamethasone, vincristine, and doxorubicin without asparaginase during induction. The regimen employs an extended consolidation in which the induction treatment is repeated during cycles 3, 5, and 7, alternating with high doses of methotrexate and cytarabine in cycles 2, 4, 6, and 8. This is accompanied by rigorous CNS prophylaxis using intrathecal chemotherapy and followed by prolonged maintenance with 6-mercaptopurine (Purinethol), vincristine (Oncovin), methotrexate, and prednisone (POMP regimen). In the trials, >90% of patients achieve CR with 3-year survival rates of 50%. Similar to BFM-style regimens, the addition to Hyper-CVAD of rituximab for CD20 positive patients and nelarabine for T-ALL patients has been associated with improved outcomes in phase 2 studies, but the results of randomized trials with these agents are awaited.

Fit adults: maintenance therapy

Despite the lack of randomized trials investigating maintenance treatment in adult ALL, 2 older trials showed inferior results compared with historical controls without maintenance therapy. Based on these data and the experience in pediatric studies, maintenance regimens mimicking those used in pediatric protocols, ie, with daily mercaptopurine and oral weekly methotrexate, often supplemented by monthly vincristine and CS pulses, are essential components of treatment for adult B and T-cell ALL.

In one randomized study, the maintenance arm with reinforcement cycles was not superior to conventional maintenance therapy (37% versus 38% at 8 years). A treatment duration of 2.5-3 years is optimal and is usually recommended.

Treatment of older Ph-negative patients

Definition and prognosis of older patients

The definition in most clinical trials is based on an age cutoff of 55-60 years, reflecting the difficulties of delivering complex multiagent chemotherapy according to schedule, and the poor prognosis of patients above this age bracket even with intensive therapy. In the UKALL XII/ECOG 2993 trial, 5-year survival of patients aged 56-65 years was only half that of younger adults (21% versus 41%) and survival becomes dismal beyond this age. Comorbidities and differences in pharmacodynamics and pharmacokinetics contribute to a high-induction mortality and a higher prevalence of unfavorable genetic features is associated with more chemoresistance. Older

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patients are also less frequently enrolled in clinical trials, or are treated in trials designed primarily for younger fit patients. There is, therefore, no standard chemotherapy treatment for "older" patients with ALL, and treatment decision are often individualized. Goals of therapy should always be guided by patient preference and advice to the patient should consider the biological, rather than the chronologic age. Standardized comorbidity scores, the hematopoietic cell transplantation comorbidity index and various geriatric assessment tools that include measures of cognitive and social function may be helpful but have not been validated for ALL and have not yet been widely adopted in routine clinical practice. Importantly, the clinician should be open to changing the therapeutic strategy during therapy, for example in response to a patient´s condition improving or deteriorating, or due to reassessment of disease-related risk factors, most prominently related to levels of MRD achieved during treatment. In general, primary consideration should be given to an age-adapted intensive regimen, and palliative care should be restricted to few very frail patients. Transplant options are discussed in the section on HSCT for adult patients.

Treatment of fit older patients

During diagnostic workup, reduction of leukocyte counts is achieved by a corticosteroid prephase, which may be combined with low-dose cyclophosphamide or vincristine. The principles of treatment including prophylactic intrathecal chemotherapy are fundamentally the same as for younger patients, with deintensification of dose-density and omission of individual agents if required. Cranial radiation therapy is not recommended. The best regimen is unknown. Omission of anthracyclines reduces toxicity during induction and is advisable in older patients, liposomal anthracyclines have yielded mixed results. Asparaginase has significant morbidity during induction which can be addressed by dose reductions or by delaying its use to postremission therapy.

A modification of the Hyper-CVAD regimen developed by MDACC, which eliminates anthracyclines, reduces cyclophosphamide and dexamethasone to 50%, and methotrexate to 25% of the dose of standard Hyper-CVAD (mini-HCVD) is often used in the United States. The European Working Group for Adult ALL (EWALL) developed a consensus treatment protocol for older patients with ALL that is based on a dose-reduced pediatric (BFM)-based chemotherapy regimen. Both of these regimens achieve CR rates in the 70%-80% range, but long-term outcome is disappointing even when the regimen can be delivered as intended. Death during induction shows an age-dependent increase from 10%-20% to nearly 40% in patients older than 75 years, with a rate of death in CR of 30%-40%. Arguably, treatment regimens for older patients best serve as established chemotherapy backbones for the addition of immunotherapeutic and other novel agents.

Targeting CD20 with the naked antibody rituximab failed to show any benefit in older patients in contrast to younger cohorts, apparently due to a higher rate of infectious complications, and is not recommended for older patients.

The anti-CD22 antibody-drug conjugate (ADC) inotuzumab ozogamicin (IO) is currently approved by the FDA and European Medicines Agency (EMA) for the treatment of relapsed/refractory BCP-ALL, based on the large randomized INO-VATE trial which randomized IO against standard chemotherapy. More than a third of the patients in this trial were older than 55 years, and rates of CR (81%) and MRD negativity 78% for CR patients) in response to IO were similar to those in younger patients. However, progression-free survival was only 5 months.

Use of IO as first-line therapy was evaluated in combined with reduced intensity mini-HyperCVD followed by 3-year maintenance therapy with dose-reduced 6-mercaptopurine, vincristine, methotrexate, and prednisone in a study in older patients (≥60 years) and compared with historical controls receiving only mini-HyperCVD. Eighty-five percent of patients achieved a CR, with no early deaths during the first 4 weeks of treatment, although nearly a quarter of patients died in CR. Several cases of VOD/SOS (Veno-occlusive disease/Sinosoidal obstruction syndrome) prompted dose reduction of IO during the course of the study. Three-year progression-free survival and OS were 49% and 56%, respectively, comparing favorably with historical controls.

Based on these encouraging data, a subsequent study evaluated clinical outcomes of older patients with newly diagnosed Ph-negative ALL treated with inotuzumab ozogamicin in combination with low-intensity chemotherapy (mini-HyperCVD), with or without blinatumomab as consolidation therapy. Results were compared to a historical control group treated with standard intensive Hyper-CVAD. The IO-HCVD ± blinatumomab regimen induced higher response rates (98% versus 88%) with lower rates of early death (0% versus 8%) and lower rates of death in complete remission (5% versus 17%). Toxicity nevertheless was significant and prompted an amendment reducing the number of cycles from 4 to 2. In patients older than 70 years, POMP maintenance was replaced by blinatumomab. With propensity score matching, the 3-year EFS (64% versus 34%) and OS (63% versus 34%) rates were superior for the antibody–low intensity hemotherapy combination. Despite these encouraging results, IO is currently approved only for relapsed ALL patients and is available for frontline therapy only in clinical trials, such

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as the European EWALL-INO trial of IO with low-intensity chemotherapy for older patients (NCT03249870).

As exemplified by these and other recent clinical studies, inducing CR is less challenging than preventing disease recurrence, indicating that postremission therapy remains inadequate. Different protocols incorporate different cytotoxic agents which in general are similar to those used for induction, and their poor tolerability typically preclude prolonged postremission therapy. It is therefore unlikely that further modifications of chemotherapy alone will impart any survival benefit on these patients.

The bispecific T cell–engaging antibody blinatumomab has shown considerable efficacy in relapsed or refractory and MRD-positive B-lineage ALL. It is not approved for newly diagnosed ALL but has recently gained approval for patients who are MRD-positive. Notably, blinatumomab seems to have similar clinical efficacy irrespective of age as judged by trial data in patients with relapsed/refractory B-cell ALL, and MRD negativity rates are likewise similar to younger patients. Cytokine release syndrome and neurological toxicities as the main serious toxicities of blinatumomab appear to be more common in older patients.

The frontline administration of blinatumumab in combination with chemotherapy is being explored in several trials directed at, or including, older patients in the US (MDACC, NCI) and in Europe. A chemotherapy-free induction and consolidation regimen with blinatumomab monotherapy followed by POMP maintenance was trialed by the SWOG (study 1318). Interim analysis demonstrated a 66% CR rate and 1-year relapse-free survival of 56%. A combination study of IO plus blinatumomab for untreated or relapsed/refractors older ALL patients is planned (NCT03739814). In the absence of a trial, administration of blinatumumab in older patients who are in CR but who remain MRD-positive after conventional age-adapted induction therapy may be considered.

Allogeneic stem cell transplantation with reduced intensity conditioning continues to remain a credible treatment option to be offered to fit older patients, although no randomized data exist that demonstrate superior survival compared with chemotherapy. Measurement of MRD may eventually inform transplant decisions in older patients but presently are available only for younger patient cohorts. There is no evidence that autologous hematopoietic stem cell transplantation provides any benefit to older patients with Ph-negative ALL.

Treatment of patients not eligible for intensive chemotherapy and transplant

For those patients older than 75 years and/or with a poor performance status, no standard therapy has been defined and study data are lacking. Purely palliative therapy is very unlikely to be of any benefit. CS and vincristine are reasonable options as long as there is heightened awareness and avoidance of peripheral neuropathy. Mercaptopurine, possibly combined with weekly low-dose methotrexate, can be given in addition (POMP regimen) if organ function permits. CNS prophylaxis in this older population should at least be considered, based on individual fitness.

CNS-directed treatment

Prophylactic therapy

Three to five percent of children and <10% of adults with ALL present with CNS leukemia, typically as meningeal involvement. A lumbar puncture at the time of ALL diagnosis is always performed in pediatric studies and is performed early but more variably timed in adult ALL regimens. The presence of CNS disease is defined by >5 leukocytes per microliter of cerebrospinal fluid (CSF) along with the presence of lymphoblasts in the CSF. As detection of ALL blasts in the CSF, even from traumatic lumbar puncture, has been associated with an increased risk of CNS relapse and poor EFS, special precaution should be taken to decrease the rate of traumatic lumbar punctures. Risk mitigation includes platelet transfusion to a platelet count ≥50 × 10^9/L for initial intrathecal treatment, having the most experienced clinician perform the procedure, and or placing the patient under deep sedation or general anesthesia as is commonly done in the pediatric setting.

In the absence of prophylactic CNS-directed therapy, CNS relapse occurs in 35%–75% of patients at 1 year. Prophylactic cranial irradiation was an instrumental part of the early success of combination trials with curative intent and thus initially became the standard treatment in children and subsequently adults. The combination of intrathecal methotrexate and 24-Gy cranial irradiation in an early adult trial demonstrated that CNS prophylaxis reduced the CNS relapse rate at 24 months from 42% to 19% when compared with no CNS treatment. The desire to reduce long-term radiation-associated sequelae, including seizures, cognitive dysfunction, early dementia, and growth stunting, which were particularly pronounced in children, has led to replacement of prophylactic cranial irradiation by intrathecal and systemic chemotherapy in nearly all pediatric protocols. In some protocols cranial irradiation has been retained for higher-risk patients, as a radiation dose of 12 Gy appears to provide adequate protection against CNS relapse even in high-risk patients (eg, those with T-cell ALL and leukocyte counts >100 × 10^9/L). However, a meta-analysis of T-cell ALL showed

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no conclusive evidence to suggest that treatment strategies including CNS irradiation (either prophylactic for all or only for risk groups or patients with frank CNS involvement) had better outcomes than with therapies completely omitting irradiation. Another meta-analysis including >16,000 patients, treated between 1996 and 2007 comparing comprehensive pediatric treatment protocols with and without CNS irradiation, found an increased risk of relapse in the small group of patients with overt CNS involvement at diagnosis but a high rate of events even in the irradiated group, suggesting that CNS irradiation did not affect the overall risk in contemporary protocols. In adults, neuropsychological adverse effects are less well studied, but myelotoxicity and acute tissue toxicities caused by combined radiation and intrathecal chemotherapy may delay postremission consolidation treatment. Therefore, cranial irradiation has been omitted as primary CNS prophylaxis from most adult ALL protocols as well. CNS relapse rates as low as 5% have been achieved without irradiation by using combination intrathecal treatment in conjunction with high-dose systemic treatment that can penetrate the cerebrospinal fluid, most notably high-dose methotrexate and cytosine arabinoside. Throughout the course of therapy, for example with the Hyper-CVAD regimen, the number of prophylactic intrathecal administrations ranges from 8 to 12, depending on age and tolerability.

No single CNS-directed prophylactic therapy has been proven to be superior to others. The combination of intrathecal methotrexate, cytarabine, and CS (termed triple therapy) may more effectively prevent relapse than intrathecal methotrexate alone but may not improve the overall outcome. A meta-analysis showed that adding intravenous methotrexate for patients treated with triple intrathecal therapy improves outcome by reducing both CNS and non-CNS relapses.

Intrathecal therapy should be intensified in patients with blasts in the CSF even if blasts are due to a traumatic lumbar puncture. Details of administration such as patients remaining in a prone position for at least 30 minutes after the procedure to enhance the distribution of the chemotherapy within the CSF and to avoid postspinal headache should be adhered to.

Together, all available evidence in children and adults emphasize the importance of prophylactic therapy for all patients irrespective of risk group, with an increasing body of evidence showing that rigorous administration of effective intrathecal and systemic chemotherapy obviates the need for cranial irradiation. Conversely, the presence of symptomatic CNS disease at diagnosis remains an indication for concurrent radiation therapy and intrathecal chemotherapy. Additionally, CNS radiation maintains an important role in the prehematopoietic transplant preparative regimen for B-ALL. HSCT regimens are, however, discussed elsewhere, in the chapter on HSCT for the treatment of leukemia.

Control of active CNS leukemia

Symptoms of CNS involvement include headache, meningism, fever, or cranial nerve palsies, but some patients may be asymptomatic. Subtle symptoms such as periorbital tingling or numbness should also alert the physician to the possibility of CNS involvement. Bowel or bladder dysfunction or neurologic deficits affecting the extremity may indicate spinal cord or cauda equina involvement and are considered an oncologic emergency, necessitating immediate workup and treatment in the form of radiation and/or chemotherapy. Cranial CT or mediastinal irradiation (MRT) imaging may be indicated to rule in CNS involvement and/or rule out other causes of neurological signs and symptoms, eg, hemorrhage, elevated intracranial pressure or an intraparenchymal lesion as opposed to the far more common meningeal involvement. Risk factors include mature B-cell ALL, high serum lactate dehydrogenase levels (>600 U/L), and the presence of a high proliferative index at diagnosis (>14% of lymphoblasts in the S and G_2/M phase of the cell cycle).

To minimize the risk of contaminating the CSF with ALL blasts by traumatic lumbar puncture, intrathecal chemotherapy should be administered with every LP. If CNS leukemia is detected, intrathecal triple therapy is given 2-3 times per week until all blasts have cleared from the CSF. Repeated, closely spaced intrathecal instillation of methotrexate may cause mucositis, necessitating prophylactic administration of leucovorin. In addition to intrathecal triple therapy, systemic treatment including high-dose methotrexate, intensive asparaginase and dexamethasone, is important to control CNS leukemia. A recently closed very large (>1800 patients) study of T-cell ALL in children and young adults (1-30 years of age) from the Children's Oncology Group has randomized high-dose methotrexate (protocol M) versus a cycle of Capizzi-style interim maintenance (increasing intravenous methotrexate without rescue, intrathecal methotrexate, vincristine, and asparaginase). The randomization was performed in the context of a backbone protocol including low-dose cranial irradiation (12 Gy) for almost all patients. In this setting, the Capizzi group fared better with an increased event-free survival (88.9% versus 83.3%) compared with the HDM group. The study also randomized the addition of nelarabine to both arms throughout postinduction therapy for medium- and high-risk patients in a factorial design;

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nelarabine improved the EFS for both groups, partly by reducing the number of CNS-involving relapses.

Hematopoietic stem cell transplantation

Allogeneic HSCT is one of the areas in which therapeutic algorithms applied to children and adults currently diverge most widely. This can be attributed to the fact that contemporary intensive protocols are curative in most children and may even be successful in relapse, whereas disease recurrence in adults is rarely salvageable without HSCT. In addition, reduced intensity conditioning regimens used for adults beyond the AYA age bracket may be more tolerable than prolonged administration of multiagent chemotherapy. Nevertheless, the advent of highly effective immunotherapies and an increasing proportion of MRD-negative patients has led to a reevaluation of HSCT, which continues to be associated with considerable nonrelapse mortality and morbidity.

Children: HSCT

With the generally improving results in primary treatment, the indications for HSCT in first remission have become more exclusive. In practice, the rate of HSCT in first remission varies among different protocols.

A very poor early response to remission induction treatment, possibly with the exception of patients aged 1-6 years with favorable leukemic cell genetics (mostly high hyperdiploidy), is an indication for transplantation in many, but not all, protocols. There is more consensus regarding patients with remaining detectable MRD at high level after consolidation, who are uniformly considered to have an HSCT indication. There are few data to suggest that cytogenetic changes only (without taking response to therapy into consideration) should be an indication for HSCT in first remission. Except in some small studies, transplantation failed to improve the outcome for infant patients with *KMT2A* rearrangement. Hypodiploid cases did not appear to benefit from transplantation, but the number of patients treated with this modality was very small.

BCR-ABL1–positive ALL was, before the advent of tyrosine kinase inhibitor (TKI) therapy, a certain HSCT indication, but also, in this genetic subgroup, transplantation is reserved for poor responders.

New modalities of immunotherapy may further reduce the fraction of B-lineage patients who will undergo transplantation, but, for poorly responding T-cell patients, HSCT will probably remain the best option for some time. It has been long debated whether children have to be conditioned with total body irradiation (TBI). To date, TBI as part of HSCT-preparative regimen for pediatric B-ALL remains the standard of care. A randomized international study has been launched to address this important issue because TBI remains a major source of serious late effects after transplantation.

An additional consideration for allogeneic HSCT is donor availability. Matched sibling donors remain the preferred donor option, as available, yet outcomes using mismatched-related, matched, or mismatched-unrelated umbilical cord and haploidentical donor sources continue to improve. Although donor sources are described in greater detail in the chapter on HSCT, it is notable that α/β T cell–depleted haploidentical donor sources with or without T-cell addback products to facilitate engraftment are gaining popularity, as outcomes have been shown to be comparable to matched unrelated donors and superior to mismatched-unrelated donor sources. With increasing donor pools, suitable donor products can be found for the majority of pediatric patients with B-ALL meeting HSCT indication.

Adults: HSCT

Traditionally, the translocations t(9;22) and t(4;11) define very high-risk populations with a clear indication for allogeneic HSCT, whereas additional criteria defining high-risk ALL (eg, low hypodiploidy, complex karyotype, Ph-like ALL, and ETP subtype) and an indication for HSCT in CR1 differ between various cooperative study groups. For several reasons, these traditional criteria underpinning transplant decisions are being reassessed: (1) a lack of definitive data showing a survival benefit from HSCT for most of these subgroups, (2) the evolving role of MRD level as the single most important risk factor, (3) the improving cure rates with pediatric-inspired intensified treatment regimens, (4) better outcomes due to improved transplant procedures and supportive care, and (5) the availability of BiTE and CART therapy. While allo-HSCT arguably remains the treatment modality with the greatest antileukemia activity, this is partially offset by high nonrelapse mortality of 20%-40% which for reasons that are unclear exceeds that expected in AML.

In recent studies of Ph-negative ALL, MRD has partially or completely replaced traditional risk factors as criteria for transplant versus no-transplant decisions, particularly in adolescents and younger adults with good MRD response in whom pediatric-inspired protocols achieve 5-year survival rates of up to 60%-70%. These studies suggest that early MRD negativity in response to chemotherapy may override clinical or even genetic risk factors formerly considered adverse, implying that MRD good responders should probably not be exposed to the risk of transplant-related mortality (TRM) in CR1.

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Conversely, patients who remain MRD positive including many initially categorized as standard-risk patients according to conventional criteria, may benefit from and should be considered for HSCT. However, a decision on whether and when to transplant will depend not only on a patient´s individual transplant risk but also on the level of MRD and the availability of alternative type of immunotherapy or experimental treatment options. Outcome after HSCT has been shown to be better in MRD-negative patients, suggesting that additional pretransplant therapy intended to achieve lower levels of MRD prior to HSCT may improve long-term outcome, although the validity of this concept has not been formally proven in prospective randomized trials. Additional caveats for these MRD-based approaches include differences in the methodology of MRD assessment, MRD timepoints, selection criteria for MRD-directed therapy, lack of standardization and differences between treatment regimens.

With the increasing availability of effective and novel treatment options, scheduling, and sequencing of therapeutic agents in relation to each other and to HSCT have become relevant issues and standards as yet mostly undefined.

In current MRD-based strategies, approximately 20% to 30% of MRD-negative patients experience hematologic relapse. In this event, salvage therapy should be used as a bridge to HSCT, which needs to be scheduled urgently as second remission tend to be short. To detect and treat molecular failure before hematologic relapse occurs, MRD testing needs to be performed frequently, at high sensitivity and with rapid turnaround of results. Because this is logistically and resource-wise challenging, there is at present no uniform approach to postremission MRD assessment, particularly after end of maintenance.

Despite a substantial and age-dependent transplant-related mortality and morbidity in adult ALL patients, the poor outcome among older patients treated with non-transplant strategies justifies considering HSCT on a case-by-case basis. Reduced intensity conditioning regimens are comparable to myeloablative conditioning in terms of OS because lower TRM generally compensates for higher relapse rates. TBI-based conditioning with 8 Gy is tolerable in older patients and will be prospectively evaluated in a randomized trial in the UK. The Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation analyzed a cohort of 142 older patients (median age, 62 years; range, 60-76 years) who underwent allogeneic HSCT in CR1 using RIC. The cumulative incidences of relapse and nonrelapse mortality at 3 years were 40% and 23%, respectively, and 3-year OS was 42%. The acceptance and tolerability of haploidentical HSCT even in older patients and availability of umbilical cord blood as an alternative source of HSCs has increased the donor pool to an extent that nearly all patients will have a donor.

Management of unique ALL subsets

BCR-ABL1–positive ALL

Principles of therapy

The frequency of Ph^+ ALL increases with age and is found in approximately 50% of patients with B-cell precursor ALL over the age of 60, whereas it is uncommon in pediatric ALL patients. Despite similarities in treating children and adults with this disease, the biology of the leukemia differs between these age cohorts. The clinical relevance of this finding primarily concerns differences in the indication for allogeneic stem cell transplantation. Treatment and outcome of patients with *BCR-ABL1*–positive ALL has changed dramatically during the past decade, following addition of the ABL-directed tyrosine kinase inhibitors to frontline therapy.

As with all other subtypes of ALL, the administration of effective CNS-directed prophylaxis to prevent CNS relapse is of critical importance. Available data suggest that intrathecal therapy is sufficiently effective, with no need for cranial irradiation.

Tyrosine kinase inhibitors

TKIs are an integral part of frontline treatment, either alone (plus CS) or added to frontline chemotherapy. They should be started as soon as the diagnosis of Ph^+ ALL is established, in adult patients, typically within 5-7 days of presentation. CR rates exceed 90% in nearly all studies irrespective of which TKI is used; TKI, in combination with chemotherapy, reduces MRD more rapidly and to lower levels than is achieved by chemotherapy alone.

The optimal choice of TKI remains to be resolved, although single-arm studies suggest that second- and third-generation TKIs may be superior to imatinib, at least in patients who do not undergo HSCT. With imatinib-based therapy frontline therapy followed by allo-HSCT, long-term DFS rates of 60%-75% have been reported. A high imatinib dose (800 mg/day) during the induction period appears to have greater efficacy than doses of 600 mg or lower. Second-generation TKIs, with more data available for dasatinib than nilotinib, have the theoretical advantages of greater potency and clinical activity against a broader panel of kinase domain mutations conferring resistance. Unfortunately, no prospective comparative trials to determine whether any TKI is superior have yet been performed in adults, and comparisons

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with historical imatinib-based studies are inconclusive, partly due to the confounding effect of HSCT. For non-transplanted adult patients, the current consensus position is that TKI should be continued indefinitely, if possible.

The third-generation TKI ponatinib has attracted particular interest not only because of its overall potency against the BCR-ABL kinase but because of its ability to inhibit BCR-ABL harboring the T315I tyrosine kinase domain (TKD) mutation, which confers resistance to all other clinically approved ABL-TKI and is the TKD mutation most frequently associated with resistance to dasatinib. Combined with the Hyper-CVAD regimen for frontline treatment of patients with Ph^+ ALL, ponatinib induced deep molecular responses in the majority of patients and was associated with excellent outcome even in patients not undergoing allogeneic SCT in the only study published to date. These data are particularly relevant for older patients with *BCR-ABL1*-positive ALL in whom allo-HSCT may be perceived as posing too great a risk. Longer follow-up will be needed, however, to confirm these promising results. Randomized comparative trials to compare regimens incorporating ponatinib or other TKIs are ongoing in the US and Europe.

The TKI approved for treating Ph^+ ALL differ in their safety profiles, but toxicity is usually manageable. Pleural and pericardial effusions and rarely pulmonary arterial hypertension are seen with dasatinib, amylase, and lipase elevations and clinically symptomatic pancreatitis have occasionally been observed in patients with a history of pancreatitis receiving nilotinib and ponatinib. Cardiovascular ischemic as well as embolic or thrombotic peripheral vascular events associated with ponatinib and nilotinib necessitate a thorough evaluation of the patients' cardiovascular status and disease history before commencing with TKI therapy. Dose reduction to 30 mg during initial therapy for Ph^+ ALL largely mitigates arterial occlusive events without compromising efficacy.

Chemotherapy regimens and dose intensity

Because upfront TKIs are so effective in inducing CR, the intensity of induction chemotherapy can be reduced without compromising the response rate, while decreasing toxicity at the same time. In a large, randomized trial conducted by the French GRAALL Study Group, more intensive induction was actually detrimental in terms of morbidity and mortality and had no survival benefit. Irrespective of age, an initial cytoreductive 5- to 7-day prephase using CS is administered to reduce the leukemic cell burden while awaiting the results of molecular classification. An induction cycle combining TKI with CS or CS plus vincristine has been adopted among others by the GIMEMA and EWALL consensus protocols for older Ph^+ ALL, respectively. With this approach, induction mortality can be nearly abrogated even in a multicenter setting.

Efforts to further minimize the toxicity of chemotherapy while maximizing effectiveness has led to evaluation of frontline therapy combining TKI with immunotherapy. A potentially practice-changing study conducted by the Italian GIMEMA study group trialed an 85-day induction period with dasatinib and CS followed by blinatumomab for up to 5 cycles, given concurrently with dasatinib. Ninety-eight percent of patients achieved a CR by the end of induction and 60% were MRD negative after 2 cycles of blinatumomab. Overall and disease-free survival was 95% and 88%, respectively, at a median follow-up of 18 months. Chemotherapy-free (except for intrathecal prophylaxis) first-line therapy for Ph^+ ALL, including combination of blinatumomab and TKI is being tested in several randomized and nonrandomized trials in Europe (EWALL-PH03; NCT04688983) and the US (EA9181, NCT04530565; SWOG 1318, NCT02143414).

In contrast to the efficacy of induction therapy, it is less certain how best to maintain remission. TKI remain a central pillar of postremission therapy, while it is somewhat controversial whether to continue consolidation with low-intensity or intensive chemotherapy or allogeneic hematopoietic stem cell transplantation. More recently, autologous SCT has been reconsidered as an option for a select subset of patients with a very good response to induction therapy. The impact of ponatinib-based therapy on these treatment decisions remains to be determined. In the only study published to date that prospectively evaluates ponatinib with chemotherapy (using the Hyper-CVAD regimen), 2-year EFS was 81%. Longer follow-up will be needed to determine whether this combination may be curative in a sizeable proportion of patients not undergoing HSCT. Long-term outcome data relying solely on TKI therapy or TKI plus only CS and/or mild chemotherapy are lacking. A high relapse makes such a nonintensive regimen an unattractive option for patients eligible for intensive treatment.

"Chemotherapy-free" regimens

The potential for immunotherapy to avoid the toxicity of chemotherapy while maintaining or even enhancing efficacy has prompted evaluation of regimens eliminating systemic chemotherapy by combining TKI with immunotherapy, most notably the bispecific T-cell engager blinatumomab. The GIMEMA conducted a trial in which an 85-day induction with dasatinib and CS was followed by up to 5 cycles of blinatumomab combined with dasatinib. Nearly all (98%) of patients achieved a CR. The molecular

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response rate increased from 29% following TKI treatment to 60% after 2 cycles of blinatumomab plus dasatinib. Adding blinatumomab also resulted in clearance of ABL1 mutations that had evolved on dastinib monotherapy. At 18 months median follow-up, disease-free survival was 88% respectively. It is noteworthy that despite conventional intrathecal prophylaxis some CNS relapses occurred, highlighting the need to intensify CNS-directed therapy. Moreover, approximately 40% of patients underwent allogeneic HSCT, confounding the outcome attributed to this chemotherapy-free strategy alone. The potentially paradigm-changing concept of first-line therapy for Ph^+ ALL based only on TKI combined with blinatumomab is being explored in several ongoing trials in older patients with Ph^+ ALL (EWALL-PH03; NCT04688983; EA9181, NCT04530565, and SWOG 1318, NCT02143414).

Risk stratification

Although Ph^+ ALL is considered a very high-risk subtype in adults several additional parameters are indicative of a particularly poor prognosis. As for Ph-negative ALL, age, WBC count > 30/nL and CNS involvement are inversely correlated with outcome, as are additional chromosomal abnormalities and supernumerary Ph chromosomes at diagnosis. More recently recurring genomic abnormalities in genes involved in B-cell development, eg, IKZF1 and CDKN2A/B deletions have been linked with less favorable outcome, including patients receiving highly effective first-line treatment with TKI plus blinatumomab or those undergoing HSCT in CR1. Current data also indicate that the number of affected genes is prognostically relevant. The suggestion that the $p210^{BCR-ABL1}$ isoform is linked to an inferior outcome has not been conclusively resolved.

MRD and kinase domain mutations

The concept of quantitating low-level measurable (minimal) residual disease as a prognostic marker and guide to therapy in ALL is well established and applies equally to the Ph^+ ALL subtype. The 3 most commonly used methodologies are qRT-PCR for BCR-ABL1 transcripts, PCR analysis of clonal immunoglobulin (Ig) and T-cell receptor gene rearrangements and MFC, the latter being more popular in the US. As these methods differ in their sensitivity, complexity, and assay variability, comparison of results is difficult or impossible. However, the primary goal of therapy is to rapidly achieve low levels of MRD, ideally to below the level of detectability with high sensitivity ($>10^{-4}$) assays.

The frequent association of clinical resistance to TKI with point mutations in the tyrosine kinase domain of BCR-ABL1 mandates rising levels of BCR-ABL1 transcripts should prompt KD mutation analysis. Depending on which TKIs is used different types of mutations predominate, and these differ in their sensitivity to individual TKI, opening therapeutic opportunities. The T315I gatekeeper mutation is the most frequent KD mutation with second-generation TKI; of currently approved TKI, only ponatinib has activity against the T315I mutation. The bispecific T-cell engager blinatumomab has also demonstrated clinical activity against TKD mutations including T315I. Therefore, clinical relapse or a significant rise in MRD should trigger testing for BCR-ABL1 KD mutations, as the results will inform subsequent therapy in relation to which TKI to switch to. NGS has become the method of choice for mutation testing, providing a sensitivity of 1%-5%.

Superiority of clinical intervention based on detectable MRD rather than at morphologic relapse has been demonstrated for blinatumomab, leading to FDA and EMA approval of blinatumomab initially for MRD-positive Ph-negative and more recently Ph^+ ALL. The concept of clinical intervention for molecular failure or relapse in Ph^+ ALL is supported by clinical trials and is applicable not only to blinatumomab.

Indications for HSCT for Ph^+ ALL in adults

Allogeneic HSCT is the best-established curative therapy for Ph^+ ALL and the gold standard against which other forms of treatment should be compared. The limitations of donor availability have been largely abrogated by bigger registries and haploidentical HSCT. Age, comorbidities, and performance status remain critical determinants in the decision to proceed or not to proceed to HSCT and will have to be judged for each patient individually because the risk of nonrelapse mortality associated with transplant remains considerable. The depth of response to therapy as determined by quantitative assessment of MRD at the time of HSCT is increasingly being recognized as an important predictor of outcome and parameter informing transplant decisions.

A small proportion of Ph^+ ALL patients, specifically those with a very good molecular response, may remain in remission for prolonged periods even without HSCT. These results have given rise to the notion that patients with low-level or negative MRD may not need to undergo HSCT to be cured, although a large proportion of MRD-negative patients eventually relapse.

This issue is most pressing in patients at higher risk of TRM due to age or comorbidities in whom the superior antileukemic efficacy of HSCT may be outweighed by early mortality. The use of MRD to inform a treatment

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decision for or against HSCT is further compounded by the lack of methodological standardization and of universally agreed MRD thresholds, which are also likely to depend on the clinical setting, including transplant modality.

Whereas autologous stem cell transplant (ASCT) has no role in Ph-negative ALL, recent albeit limited data indicate it may have potential utility in patients who achieved molecular remission and are not eligible for allogeneic HSCT. In the prospective GRAAPH-2005 trial, survival after ASCT and allo-HSCT was identical in a subset of patients with low MRD levels (BCR-ABL1/ABL1 ratio ≤0.01%). A randomized comparison of these treatment modalities should be awaited before routinely adopting ASCT as therapy for Ph^+ ALL.

Patients treated outside of clinical trials should be assessed frequently for MRD, and rising levels should prompt an intervention, including checking for presence of TKD mutations, reconsideration of HSCT, and/or intervention with a non-TKI modality, eg, blinatumumab. Donor lymphocyte infusions have had very limited, if any, success in preventing relapse, probably due to the typically rapid relapse kinetics of Ph^+ ALL.

Posttransplant TKIs in adults

Whereas TKIs are used universally as part of therapy leading up to HSCT, the role of TKI administration after transplantation has been studied less extensively, and the overwhelming body of data is based on use of imatinib. In a large retrospective registry analysis and across the majority of small prospective trials, use of imatanib after HSCT was associated with a lower relapse rate and better outcome compared with historic controls. The only randomized clinical trials addressing posttransplant TKIs demonstrated excellent long-term survival with both a prophylactic and a preemptive MRD-triggered administration of imatinib. Thus, 1 of these 2 approaches should be considered as the standard in the posttransplant setting. MRD should be monitored frequently, preference should be given to BM as a source of material, and close attention should be paid to the assay sensitivity.

In patients not undergoing HSCT, TKIs should be given indefinitely as maintenance therapy, even in case of prolonged undetectable MRD.

Ph^+ ALL in pediatric patients

In pediatric patients with BCR-ABL1–positive ALL, survival has improved from about 40% to approximately 70% with the use of imatinib. In a randomized study comparing dasatinib with imatinib in the context of intensive chemotherapy in pediatric and adolescent patients up to 18 years of age, dasatinib given at 80 mg/m^2 per day was more effective than imatinib at 300 mg/m^2 per day in improving event-free and overall survival. The SCT-rate has varied between studies, and there is general agreement that high MRD should be used to select patients that should be transplanted, but the background data for MRD-based stratification are not perfect and will be continuously monitored in planned studies. The addition of TKIs to intensive high-risk chemotherapy has been associated with considerable treatment-related mortality, and studies are planned to randomize patients between backbones of different intensity to complement the TKI therapy, somewhat akin to adapted therapy for the older patients. So far, post-HSCT TKI therapy has been limited (to about a year) in the pediatric setting. Interestingly, TKIs have properties that invoke CAR T-cell resting and practice regarding integration of TKIs in the post-CAR setting have not yet been established. Dasatinib in rare cases has been used in event of CAR toxicity due to preclinical evidence that dasatinib abrogates CAR-mediated cytotoxicity.

Treatment of relapsed Ph^+ ALL

Relapse remains the main cause of treatment failure in patients with Ph^+ ALL, and, if occurring during TKI therapy, is most often associated with presence of a TKD mutation. Such mutations may predate the start of TKI treatment but are not identified by routine methodologies for mutational analysis. However, rising levels of BCR-ABL transcripts should prompt mutation analysis and an appropriate intervention to prevent modification of therapy before overt hematologic relapse occurs because the latter carries an ominous prognosis with median survival of about 6 months.

Switching to a (different) second- or third-generation TKI (eg, dasatinib, nilotinib, or ponatinib) depends on which TKIs were used previously and the result of mutational analysis. In the absence of mutation data, ponatinib has the greatest chance of inhibiting the malignant clone. Switching is recommended but is likely to be of only short-term benefit.

Immunotherapy strategies are the same as for other B-lineage ALL and are discussed in that section.

Ph-like/BCR-ABL1-like ALL

From the beginning, patients with BCR-ABL1-like ALL were recognized as having inferior survival, due to a lower CR rate, higher MRD levels after induction, and more frequent relapses than other patients in the same age bracket. There are conflicting data on whether this inferior prognosis can be overcome by intensified, risk-adapted

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regimens. In adolescents and young adults treated in the pediatric-inspired CALGB10403 trial, Ph-like signature and obesity were associated with inferior survival rates. All studies reported to date on adult cohorts agree that patients with BCR-ABL1-like ALL have a lower survival probability, but as in children it remains unclear whether intensive treatments are capable of ameliorating the negative impact of this subtype. This was addressed in adult ALL patients intensively treated in the pediatric-based, MRD-driven LAL1913 GIMEMA frontline protocol for adult Ph-negative ALL. This study demonstrates that Ph-like patients have a significantly lower CR rate, EFS and DFS, as well as a greater MRD persistence despite treatment in a pediatric-oriented and MRD-driven adult ALL protocol, reinforcing the need for alternative therapeutic interventions other than treatment intensification.

Theoretically, most alterations in Ph-like ALL can be targeted by FDA-approved TKIs: JAK-STAT signaling (JAK inhibition); ABL-class fusions (ABL inhibitor); and FLT3 and NTRK3 fusions (FLT3 and NTRK3 inhibitor). Some of these (ruxolitinib, imatinib, dasatinib, ponatinib) are being tested in frontline studies. Combination of kinase inhibitors against multiple signaling shows synergistic effect in patient-derived xenograft models and may provide an opportunity for well-tolerated, highly effective therapy given in addition to established treatment regimens. Considering the heterogeneity of lesions observed and consequently small number of patients, design of trials to demonstrate efficacy are challenging.

ETP-ALL

Studies investigating therapy for ETP-ALL are limited in number and size but generally noted chemoresistance and poor outcome. The use of intensive risk-adapted regimens has been credited with mitigating the inferior outcome in children, but whether this has an impact in adult patient is uncertain, resulting in a lack of clarity on what constitutes the optimal treatment regimen for ETP-ALL. Allogenic HSCT is recommended for adults with high-risk features including ETP-ALL and data from the GRAALL studies suggest a trend toward better OS with HSCT in this high-risk population. Haploidentical HSCT is a credible option but 4-year OS for ETP-ALL patients was reported as 36% and 33% with and without censoring at allo-HSCT. Thus, while implementation of allo-HSCT in CR1 seems to confer a survival benefit in adults, it is not certain that it abrogates the negative prognostic impact of ETP-ALL.

The observation that ETP-ALL exhibits alterations in JAK-STAT, FLT3, and Ras signalling pathways suggest that they may be sensitive to inhibition of FLT3 and/or JAK and/or MAPK inhibition. activity as monotherapy but did not eradicate ETP-ALL blasts. A clinical trial for relapsed/refractory ETP-ALL patients combines ruxolitinib with vincristine, prednisone, and l-asparaginase (ClinicalTrials.gov identifier: NCT03613428).

Venetoclax is an oral inhibitor of the Bcl-2 family of proteins and is approved for AML and chronic lymphocytic leukemia. Preclinical data suggest that ETP-ALL are exceptionally sensitive to BCL2 inhibition. A few clinical reports have indicated that venetoclax can exhibit activity in ETP-ALL, with a focus on combination with chemotherapeutic agents such as decitabine, bortezomib, vincristine, or combination regimens. More extensive series and prospective studies are needed to determine efficacy and emergent toxicities.

Acute leukemias of ambiguous lineage and mixed-phenotype acute leukemia

Definition and epidemiology

In a rare (<4%) subset of acute leukemias now classified as ALAL in the revised fourth edition of the WHO classification, more than 1 lineage can be assigned to the leukemia. Most subentities under this umbrella are labeled mixed-phenotype acute leukemia with addition of a specification describing their lineage mix, ie, B/myeloid (the largest subgroup), T/myeloid MPAL, and MPAL, not otherwise specified (NOS), but acute undifferentiated leukemia also belong under ALAL. A second classification systems for MPAL/ALAL that remains in use internationally is the European Group for Immunological Characterization of Acute Leukemias. Reported treatment results are confounded by important differences in the definition of MPAL by these 2 classification systems, resulting in overlapping but distinct patient populations. The WHO classification uses a limited set of lineage markers in conjunction with genetic drivers and/or a clinical context clearly defining a leukemia entity; thus, the diagnosis of MPAL/ALAL generally also requires absence of a genetic driver mutation that defines a recognized WHO leukemia diagnosis. However, some rearrangements that act as leukemogenic drivers are consistent with a diagnosis of MPAL/ALAL, for example *BCR-ABL1* (called MPAL with *BCR-ABL1, <25% of MPAL/ALAL), ETV6-RUNX* and *KMT2A* rearranged (<10% of cases) Overall, MPAL/ALALs are frequently associated with adverse genetic features.

Therapy for MPAL/ALAL in adults

Adult patients with MPAL/ALAL have a worse prognosis than other AML or ALL cohorts, with epidemiological studies from the SEER database and from United States Medicare data indicating that survival was age-dependent with older patients (≥60 or ≥65 years) showing

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2-year OS of <20%. The clinical decision of whether to choose an AML- or ALL-type regimen as frontline treatment has been largely resolved, with most studies addressing this issue demonstrated better results with ALL-like induction or combined ALL-AML therapies. Tyrosine kinase inhibitors should be added for BCR-ABL–driven leukemias. There is an absence of high-quality prospective studies to guide treatment decisions but allogeneic SCT in CR1 is recommended as the default option in patients with MPAL/ALAL, based on a more favorable outcome compared with chemotherapy alone that was not limited to very young patients. In patients who have relapsed and reachieved remission, alloSCT in CR2 may yield similar results to their non-MPAL/ALAL counterparts with AML or ALL.

MPAL/ALAL in children

In pediatric MPAL/ALAL, a recent report compiling the experience from 575 cases treated in 24 countries revealed a few important conclusions: As in adults, patients responding to ALL therapy fared better than patients treated with AML-style treatment, and this difference was particularly pronounced if the patients were at least partly positive for CD19. HSCT did not confer an obvious advantage to patients responding to ALL therapy, whereas patients treated with AML-style therapy appeared to have an advantage with transplantation.

Treatment for relapse

Epidemiology and risk factors at relapse

Twenty percent to 60% of adult patients and 15%-20% of pediatric patients will experience relapse, defined by morphological criteria, after current frontline treatment protocols. With increasing sensitivity of leukemia detection by MFC and sequence-based assays, disease response and relapse increasingly rely on MRD-based definitions that will supersede morphologic criteria.

Treatment results are much worse at relapse than at primary diagnosis, a difference that is more pronounced in adults.

Time to relapse is the strongest predictor of failure in both children and adults, but definitions of early relapse differ. With contemporary risk-adapted, intensive regimens the T-cell immunophenotype no longer appears to confer an inferior prognosis with the exception of ETP-ALL. Disease dynamics are often much more pronounced in patients with T-ALL than with B-lineage ALL, posing significant clinical challenges. Relapse in an extramedullary (EM) site (CNS, testes, lymph nodes, liver, spleen, skin, or other organs) is usually associated with poorer outcome. Seemingly isolated EM relapse can be associated with detectable MRD in BM and or peripheral blood. In fact, MRD that is consistently detected in blood but not the BM should alert the clinician to the possibility of EM leukemia. Importantly, submicroscopic bone marrow involvement at a level of 0.01% (10^{-4}) or higher by PCR at the time of overt EM relapse confers a worse outcome than in cases where bone marrow MRD is negative.

Principles of management in children

The prognosis of relapse is predicted by site of relapse, length of remission, and immunophenotype. Cure may be achieved with intensive chemotherapy alone, particularly in B-lineage, late, combined, and EM relapses. Upon relapse, it is vital to recharacterize the leukemia as leukemia may have evolved in response to treatment and disease may be clonally and genetically distinct from the diagnostic sample. A critical aspect to characterizing relapse relates to timing of relapse from diagnosis. In pediatrics, early relapse is defined as <36 months from initial diagnosis for isolated or combined bone marrow relapse or <18 months from initial diagnosis for isolated EM relapse and confers an inferior prognosis. Late relapse occurs ≥ 36 months from diagnosis for isolated or combined marrow disease or ≥18 months from initial diagnosis for isolated EM relapse may still be chemotherapy-responsive and can in some circumstances be salvaged with chemotherapy alone. Bone marrow involvement confers a worse prognosis as compared to isolated EM disease.

The preferred treatment for B-ALL in first relapse has traditionally been to put patients on a clinical trial where available, and where unavailable, to pursue chemotherapy as per prior relapsed B-ALL regimens, with principles of reinduction often reliant on reintroducing standard induction agents (including vincristine, steroids, and PEG-asparaginase, commonly with an anthracycline backbone). Patients with EM disease require systemic therapy, often with additional local control measures, most commonly in the form of radiation therapy. Patients with Ph positive disease receive tyrosine kinase inhibition in addition to systemic chemotherapy. Many protocols have so far advocated the addition of prophylactic cranial irradiation for patients treated with chemotherapy, for patients not receiving total body irradiation in their conditioning for HSCT, and also for patients without CNS involvement because of the higher risk of CNS recurrence in this situation and the overall higher risk of therapy failure.

All high-risk cases (all very early isolated BM relapses and all BM-involving relapses in T-cell ALL) have HSCT as a first option and a poor outcome if transplantation

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cannot be achieved. HSCT is also prescribed for early EM and combined relapses. Remaining MRD after initial therapy is used to select patients for HSCT in B-lineage cases of late bone marrow and combined relapses and MRD-negative cases go on to intensive chemotherapy, followed by continuation maintenance as in the primary protocols.

In the era of available targeted antibody-based therapies, there are now many additional options beyond standard chemotherapy including antibody-based blinatumomab and inotuzumab. These agents are often used as a bridge to HSCT, although CAR confers the possibility of lasting remission in some. Several large pediatric relapse programs include the ongoing multinational IntReALL study and protocols organized by the Children's Oncology Group. With FDA approval of a succession of targeted agents with overlapping indications, including blinatumomab, inotuzumab and CAR T-cell therapy, it is imperative that we study how to sequence these agents, how to combine these therapies with chemotherapy and HSCT and identify specific subsets of patients likely to benefit from specified combinatorial approaches.

Treatment of relapse in adults

Allogeneic HSCT is the only realistically curative option in relapsed adult patients, but cure is realized in only a minority of patients. If >18 months has elapsed since achieving CR (commonly referred to as late relapse), a repeat of the same initial induction regimen is warranted to achieve a second remission. Other commonly used salvage regimens for relapsed/refractory ALL include high-dose cytarabine combined with an anthracycline or mitoxantrone, the FLAG-Ida regimen (fludarabine, high-dose cytarabine and filgrastim with idarubicin), or HD MTX plus HD-AraC-based treatment blocks. Liposomal vincristine (Marqibo) has been approved for adult patients with Ph-negative ALL in second or greater relapse but has no significant role in a potentially curative approach.

In patients with relapsed or refractory T-ALL, nelarabine, a deoxyguanosine analog prodrug, is approved as single-agent therapy with proven favorable results. The CALGB used nelarabine to treat relapsed and refractory patients and demonstrated a CR rate of 41% and OS rate of 28% at 1 year. These results are especially impressive given that many of the patients had failed 2 or more inductions or had not achieved CR with their last induction regimen. A German study with nelarabine showed similar results. Despite this difficult to treat patient population, nelarabine allowed patients to proceed to transplantation and achieve increased survival. Overall, chemotherapy as first salvage therapy induces a second CR in only about 40% of cases, with a median CR2 duration of about 3 months, median OS of about 6 months, and a 3-year survival rate of 11%.

Immunotherapy

Principles of immunotherapy

Survival outcomes following chemotherapy in upfront pediatric and adult B-ALL have remarkably improved with dose intensification, combinatorial optimization, and improved supportive care. Outcomes in the relapsed/refractory setting remain dismal as previously described in this chapter. Strategies to recruit the immune system or redirect or arm immune components to target B-ALL have fallen into favor due to demonstrated efficacy. In particular, targeting surface pan–B-cell markers, including CD19 and CD22 have achieved striking responses leading to expedited drug development and FDA-approvals. We review the following approaches:

- Bispecific T cell–engaging antibodies targeting CD19 (blinatumomab, FDA approved for both adult and pediatric B-ALL)
- Antibody-drug conjugate targeting CD22 (inotuzumab, FDA approved for adult B-ALL and in development for pediatric B-ALL)
- Chimeric antigen receptor (CAR) T cells (CD19-targeting CAR T cells are FDA approved for pediatric B-ALL and in development for adult B-ALL. CD22-targeting and bispecific CAR T cells remain under development.)

There is overlapping indication for these targeted approaches and not a clear standard as to how these therapies should be sequenced or integrated into chemotherapy or HSCT regimens. Ongoing study to establish specific indications optimized for a specific approach is necessary to better understand how to harness this new class of therapy within our B-ALL armamentarium. Studies exploring immunotherapy use in the upfront setting as opposed to strictly the relapsed/refractory setting are also in process.

T-ALL

Due to the challenge of fratricide in using T cells to target T-cell leukemia, and more profound, intolerable immune suppression and toxicities in on-target, off-tumor elimination of T cells, immune-based therapy and targeted approaches for T-ALL lag in clinical development. Although there are early efforts, including a novel trial targeting CD7 in T-ALL, using CAR T cells genetically edited to disrupt CD7 expression, data remain limited in the T-ALL immunotherapy domain and the

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majority of this section thus focuses on targeted immunotherapy for B-ALL.

Immunotherapy with bispecific T cell–engaging antibody

In the development of new monoclonal antibody constructs for B-ALL, the bispecific T-cell engager blinatumomab has showed promising results in relapsed and refractory cases of CD19-positive B-precursor ALL and is approved for that indication. In a multicenter trial for 189 relapsed/refractory BCP-ALL, the composite CR rate was 43%, with a median OS of 6.9 months. Very similar results were obtained in the randomized TOWER study of 405 patients with recurrent or refractory Ph-negative ALL who were randomized to receive blinatumomab or standard chemotherapy, with CR rates of 44% versus 25% and median OS of 7.7 months versus 4 months. Predictors of response, including lower bone marrow blasT cell counts, EM disease, a high frequency of circulating inhibitory regulatory T cells (Tregs), and expression of PD-L1 on B-cell blasts, have been associated with a poor response.

Single-agent blinatumomab showed comparable antileukemia activity in a phase 2 trial of patients with Ph^+ ALL who had relapsed or were refractory to TKIs. During the first 2 cycles, 36% of patients achieved CR/CRh, including 4 of 10 patients with the T315I mutation. Median relapse-free survival and overall survival times were 6.7 and 7.1 months, respectively.

In a pediatric phase 1-2 trial that treated 93 patients with relapsed/refractory B-lineage ALL, 70 were evaluable after treatment at the finally recommended dose-level. Thirty-nine percent of heavily pretreated patients achieved CR and half were MRD-negative. About a third of the patients could go on to HSCT. Recent pediatric B-ALL data demonstrate that patients with ≥5% lymphoblasts achieve a 59% CR rate within 2 cycles of blinatumomab as compared to patients with <5% blasts, where an MRD-negative CR rate of 92% was achieved. Further validation with larger sample size will be useful; however, these findings support improved results in patients treated with decreased tumor burden. Longer-term follow-up from a phase 1-2 multicenter single-arm pediatric blinatumomab study ($N = 70$) demonstrates a 24-month Kaplan-Meier estimate of overall survival of 25% with a median OS of 7.5 months, with allogeneic HSCT associated with a positive effect on OS.

In view of the short response duration and OS in both adults and pediatrics, it is recommended that patients achieving a CR proceed to HSCT as soon as possible, using blinatumomab as a bridge to transplantation. Efforts to improve the results of blinatumomab treatment prompted earlier administration in patients still in CR but with detectable MRD. In a recent update, 78% of patients achieved a complete MRD, most after the first treatment cycle. Relapse-free survival at 18 months was 53%, and median overall survival was 36.5 months. Complete MRD response was associated with a significantly longer relapse-free survival (23.6 versus 5.7 months); overall survival (38.9 versus 12.5 months) compared with MRD nonresponders. Estimates of relapse-free survival at 18 months were similar with or without censoring for postblinatumomab HSCT and chemotherapy.

Additional trials moving blinatumomab further forward to frontline therapy are ongoing and in preparation. As with other T-cell therapies, strict attention has to be paid to a set of unique toxicities including neurotoxicity (eg, seizures, encephalopathy) and cytokine release syndrome that requires close monitoring and prompt intervention.

Immune-directed chemotherapy

Inotuzumab (IO), a CD22 antibody conjugated to calicheamicin, an enediyne antitumor antibiotic, has shown a composite CR rate of 49% in a single-institution study for relapsed/refractory B-ALL whether given on a weekly or bimonthly schedule. IO has shown activity in adults with relapsed/refractory ALL, including those enrolled in a global, open-label, phase 3, randomized trial (INO-VATE). In this trial, 326 adult patients with relapsed or refractory ALL were assigned to receive either IO or standard intensive chemotherapy (standard therapy group). In the primary intention-to-treat analysis of the first 218 patients, significantly more patients in the IO group achieved CR (80.7% versus 29.4%) and had results below the threshold for minimal residual disease (0.01% marrow blasts) (78.4% versus 28.1%).

In the survival analysis including all 326 patients, progression-free survival was significantly longer with IO (median, 5.0 months versus 1.8 months). While overall survival was only marginally longer, more patients in the IO group underwent allo-HSCT, a subgroup of whom experienced prolonged *leukemia-free survival*. Clinically relevant nonhematologic adverse events with IO were hepatotoxicity, with a significantly higher rate of veno-occlusive disease compared with the standard therapy group (11% versus 1%). Sinusoidal obstruction syndrome was most conspicuous among patients who proceeded to HSCT, with a dual-alkylator conditioning regimen constituting a significant risk factor. In a post hoc analysis to evaluate IO efficacy and safety in older patients versus younger patients treated in the randomized INO-VATE trial, CR/CRi rates with

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IO were similar in patients aged ≥55 years and patients aged <55 years (70% versus 75%, respectively). Among IO responders, the MRD negativity rate was similar among older and younger patients (79% and 76%, respectively). A phase 2 trial studying inotuzumab in children and young adults with relapsed/refractory B-ALL ($N = 48$), run through the Children's Oncology Group, achieved a CR/CRi rate of 58%, with 65% of evaluable responders having MRD responses of <0.01%. This trial was notable for a heavily pretreated cohort with a high baseline disease burden (median bone marrow lymphoblasts of 81%). Sinusoidal obstruction syndrome occurred in 8.3% of overall patients, and increasingly seen in 30.7% of patients proceeding to HSCT postinotuzumab. Sinusoidal obstruction syndrome was managed with supportive care and defibrotide and quickly resolved in all but 1 patient. Based on reported efficacy and tolerability, inotuzumab is being evaluated in a randomized phase 3 trial in newly diagnosed pediatric patients with high-risk B-ALL.

Immunotherapy with chimeric antigen receptors (CAR T cells)

Targeted immunotherapy using autologous chimeric antigen receptor T cells has proven to be a highly potent antileukemic modality in the setting of relapsed or refractory ALL. CAR constructs contain the variable binding regions of an antibody fused to the activation, costimulatory and anchoring regions of the T-cell receptor. Retroviral and lentiviral methods are most frequently used to transduce an autologous T-cell product to express the CAR receptor, thereby arming the T cell to be redirected to tumor-associated antigens and upon binding, exert CAR T-cell–mediated tumor eradication. The most frequently studied CAR constructs contain the variable region of an antibody against the pan–B-cell antigen CD19, conferring B-cell specificity, linked to the CD3ζ activation domain and either 4-1BB or CD28 costimulatory domains, with 4-1BB shown to facilitate greater T-cell persistence and more durable outcomes in B-ALL. Although CD19-specific CAR T cells have had the most expansive experience to date, CARs directed against other cancer-associated antigens, are under development and in early phases of clinical development.

CD19-specific CAR T cells have been at the forefront of CAR development for B-ALL and have mediated striking responses in the relapsed/refractory B-cell ALL setting. Complete remission rates of 60%-90% have been consistently achieved across studies and CAR constructs in both the pediatric and adult B-ALL setting, including ALL relapse following SCT. The largest multicenter global phase 2 pediatric study, ELIANA, achieved an 81% CR rate and served as the registration trial that led to the FDA approval of tisagenlecleucel (Kymriah), CD19-specific CAR T-cell therapy, in August 2017. Tisagenlecleucel was initially approved for patients ≤ 26 years, with refractory B-ALL or B-ALL in 2nd or greater relapse. In October 2021, the FDA granted approval for Tecartus (brexucabtagene autoleucel) for the treatment of adult patients (18 years and older) with relapsed or refractory B-cell precursor ALL. The CTLO19 CD19-specific CAR construct (tisagenlecleucel) that is FDA-approved for treatment of pediatric and young adult patients (aged 3 to 25 years) with B-cell precursor ALL that is refractory or in second or later relapse is undergoing dosing adjustments and toxicity evaluation in the adult setting. The clinical experience across children and adults identified CAR-specific toxicity syndromes that can range in severity from mild to fatal and have distinct management. Cytokine release syndrome and neurotoxicity (also referred to as immune effector cell-associated neurotoxicities [ICANs]) are the most common CD19-specific CAR-associated toxicities. Early clinical trials report severe cytokine release syndrome (CRS)/ICANs requiring intensive care treatment in >30% of patients. Improved understanding of toxicity management, using IL-6 receptor inhibition with tocilizumab and more liberalized steroid use has improved tolerability of these syndromes. Tocilizumab use in established-CRS has been shown to disrupt CRS without abrogating CAR efficacy. Tocilizumab, although first-line in CRS, does not cross the blood-brain barrier and steroids therefore play a vital role in managing severe CAR-mediated neurotoxicity.

We have learned that low disease burden in adults and pediatrics (<5% bone marrow blasts) before treatment associates with enhanced remission duration and survival. In addition, a higher disease burden (≥5% bone marrow blasts or EM disease) confers a greater incidence of CRS and neurotoxic events. Patients with persistent CAR T cells remain B cell–depleted and often require immunoglobulin substitution. B-cell aplasia has been used as a surrogate marker for CAR persistence and prolonged B-cell aplasia is a desirable outcome.

The clinical course of CAR delivery is similar across pediatric and adult patients, initially requiring patient to undergo leukapheresis to collect a T-cell product. T cells must undergo manufacturing, which most often involves virus-mediated transduction. For FDA-approved commercial agents, manufacturing is performed centrally (ie, tisagenlecleucel is manufactured at Novartis) and often requires a 3- to 6-week manufacturing window. For investigational CAR T-cell products, manufacturing

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may be done locally and can be performed in as little as 1- to 2-week windows. Once the CAR is manufactured, patients receive lymphodepleting (LD) chemotherapy to allow for homeostatic expansion of the incoming CAR T-cell product. Fludarabine and cyclophosphamide have become the standard-of-care LD agents and are well tolerated and can be delivered over 3-4 days in the outpatient or inpatient setting, LD has been shown to be critical to achieving efficacious CAR-mediated outcomes, and studies performing CAR therapy in the absence of lymphodepletion have had inferior outcomes. CAR infusion follows LD therapy and can also be safely performed in the inpatient or outpatient setting, pending additional patient considerations. CAR delivery involves a single-IV infusion and is generally well tolerated. Toxicities and efficacy evolve over the next 28-day window, when CAR T cells are expanding in vivo in response to antigen exposure, and mediating antitumor response. Best response is evaluated using a bone marrow aspirate following 28 days. In event that patients achieve CR, patients can opt to undergo surveillance and they can continue to observe for ongoing CAR persistence, B-cell aplasia and remission, or they can proceed to autologous stem cell transplant.

Although CAR responses have been remarkable, longitudinal follow-up has identified that the likelihood of maintaining relapse-free survival declines with time. The pediatric ELIANA trial demonstrates despite a CR rate of 81%, at 1 year following CAR infusion, the event-free survival lags at 51%. Most common patterns of relapse include relapse with ongoing CD19 expression in context of CAR T-cell loss, or relapse with associated loss of CD19 on the leukemic cells. To circumvent the latter cause of resistance, CARs targeting alternative antigens, such as CD22, and dual CARTs, targeting 2 antigens simultaneously, for example, CD19 and CD22, are being developed. CARs targeting CD22 have mediated comparable response rates to CD19-specific CAR T cells in B-ALL in the largest single-center phase I CD22 CAR T-cell trial, with a reported CR rate of 70%. Trials delivering CD22–CAR T cells have since begun enrolling at additional centers. The toxicity profile overlaps with CD19–CAR T cells with CRS and neurotoxicity, albeit decreased neurotoxicity rates. Hemophagocytic lymphohistiocytosis (HLH) has been reported with increasing frequency following CD22-specific CAR T cells, with anakinra recommended for CAR-mediated HLH. CD22 downregulation has been reported as a predominant mechanism of relapse following CD22–CAR T cell delivery.

Across the B-ALL CAR T cell experience, predictors of CAR response, persistence and relapse have yet to be validated. Efforts are ongoing to optimize CAR construct design, identify novel targets, study antigen and CAR density as related to CAR efficacy and antigen downregulation and characterize CAR phenotype, function, and exhaustion status to identify predictors and drivers of durable outcomes, These efforts will hopefully drive next-generation CAR T-cell trial design and further enhance durability of CAR-mediated outcomes.

Management of EM disease

Children and adolescents

Isolated late EM relapse with MRD-negative bone marrow at relapse diagnosis has the best outcome, also without HSCT. Relapses in sanctuary sites (the CNS and testicles) may be seen as a failure of standard therapy to adequately reach these sanctuaries and which may be rescued with local therapy with irradiation, although systemic therapy has to be administered as well.

The outcome of isolated CNS relapse depends partly on duration of CR1 and partly on whether CNS irradiation was previously performed. Outcome is worse if irradiation has already been used in primary therapy.

For patients with bilateral testicular relapse, local irradiation (22-26 Gy) is usually recommended. In patients with unilateral testicular relapse, some leukemia therapists advocate unilateral orchiectomy with reduced irradiation (15-18 Gy) to the "uninvolved" testicle, but others would rely on intensive chemotherapy alone to spare testicular function. In a recently published compilation of cases from the Children's Oncology Group, similar overall survival rates were reported between patients treated with and without the use of any testicular irradiation.

CNS radiation being removed from many pediatric protocols.

In considering more novel agents, it is critical to understand blood-brain barrier penetration, as certain agents with blood brain barrier (BBB) penetration may specifically be selected for patients with CNS3 disease. Agents without BBB penetration should not necessarily be eliminated in context of CNS disease, as they can be used in concert with intrathecal therapy.

Adults

CNS relapse in adults is associated with a very poor prognosis and often precedes systemic relapse. Median survival is in the range of months. Cranial nerves are often affected so rapid action is essential to preserve neurological function. Intrathecal chemotherapy with dexamethasone, methotrexate, and cytosine arabinoside, in addition to cranial radiation therapy (24-30 Gy), is the initial mainstay of treatment. Intrathecal administration does

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not necessarily achieve sufficient drug concentrations at the base of the brain; concentrations may be improved by intraventricular administration via an Ommaya reservoir. Additional systemic treatment employs high-dose methotrexate and cytarabine as CNS-penetrating drugs in patients with Ph^+ ALL. Dasatinib has shown some activity and can be added to the above interventions. All patients should be considered for allogeneic HSCT if possible.

EM relapse, other than in the CNS, usually involves soft tissue, lymph nodes, and skin, may occur concomitantly with or herald systemic relapse, and is a relevant clinical problem particularly after HSCT. Systemic chemotherapy, followed by allogeneic HSCT, including second HSCT if possible, is the most effective therapeutic strategy.

It is noteworthy that isolated EM (including CNS) relapse may occur despite MRD negativity in BM analysis or complete donor chimerism after HSCT.

Immunotherapy for EM disease

Antibody-based therapies, including blinatumomab and inotuzumab are known to have poor BBB penetrability, and therefore should be used in conjunction with intrathecal therapy. Concurrent or prior history of EM ALL, whether CNS or non-CNS, are associated with lower response to blinatumomab. Moreover, prior history of EM-ALL were associated with EM-ALL at the time of blinatumomab failure. Despite the lower efficacy of blinatumomab in patients with EM sites, a treatment attempt is warranted, typically in combination with other agents. In patients with Ph^+ ALL, TKIs are added after appropriate selection, based on prior therapy and mutational status. Dasatinib is the only TKI known to have CNS activity, but its use does not abrogate the need for additional CNS-directed therapy.

Cellular therapies such as CAR T-cell therapy have been shown to have good BBB penetration and are able to induce CR in patients with CNS involvement irrespective of disease burden. A high CNS leukemia burden prior to CAR T-cell infusion may however cause severe neurotoxicity requiring intense intervention. Whether or not CAR T-cell–induced remissions are sustained has not been established, owing to the small number of patients investigated and short follow-up. In one study, the initial response of CNS disease to CAR T cells was substantially higher than of non-CNS EM ALL, with a CR rate similar to that of patients without EM-ALL. However, relapse-free and overall survival were significantly inferior irrespective of the type of EM involvement. This suggests that HSCT should be considered in CART-induced remissions of EM-ALL.

Supportive care and early and late complications of therapy

Initial management

Optimal management of patients with ALL requires careful attention to supportive care because this will impact treatment results. Hyperuricemia and hyperphosphatemia with secondary hypocalcemia are frequently encountered at diagnosis, sometimes even before chemotherapy is initiated, especially in patients with high leukemic cell burden and those with T-cell or mature B-cell ALL. It should be noted that a large tumor burden per se should not unduly delay the start of chemotherapy. Typically, appropriate measures to counteract tumor-lysis syndrome are administered at the same time as therapy is started. Patients should be hyperhydrated with intravenous fluids (3000-4500 $mL/m^2/day$) to maintain diuresis and to dilute harmful metabolites. If impaired kidney function is manifested or if the tumor burden is very high and initial treatment has to be rapidly administered to stop progression of the disease, rasburicase (recombinant urate oxidase) should be given to patients at high risk of tumor-lysis syndrome to treat or prevent hyperuricemia; allopurinol may be sufficient if urate concentration is moderately elevated, and the risk of tumor lysis is lower. With rasburicase available, there is no indication for alkalinization of urine. A phosphate binder, such as aluminum hydroxide, lanthanum carbonate, or sevelamer, should be given to treat or prevent hyperphosphatemia. Calcium acetate or calcium carbonate may be used if the serum calcium concentration is low, but such treatment is seldom necessary if no alkali is administered.

Infection and antimicrobial prophylaxis

Infections are common both in patients with newly diagnosed ALL as well as in those who are already receiving therapy. During induction as well as during continued therapy, infectious complications can be fatal. Therefore, any patient with ALL who presents with fever, especially those with neutropenia, should be given broad-spectrum antibiotics until infection is excluded. Usually, all patients with ALL are given either trimethoprim-sulfamethoxazole, atovaquone, dapsone, or inhaled pentamidine as prophylactic therapy for *Pneumocystis jirovecii* pneumonia. Some pediatric and many adult trials also recommend some form of antibacterial, antiviral, and antifungal prophylaxis in patients with severe leukopenia during the intensive phases of treatment. The use of high-dose CS, in particular prolonged dexamethasone, predisposes patients to septicemia and fungal infections. The incidence of different types of infection

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may differ by center so prophylaxis practices are not uniform. The importance of prevention or early treatment is not only related to the threat of the infection itself but also to the detrimental effect of delaying antileukemic therapy.

The use of hematopoietic growth factors for adults with ALL has been found to be safe and, in some studies, has reduced the number of induction deaths, although they do not affect OS or DFS. The goal is to shorten the period of neutropenia to prevent possibly fatal infections, which are the main cause of death during induction and to facilitate more rapid progression to postremission therapy. In the Leucémie Aigüe Lymphoblastique de l'Adulte (LALA)-94 trial, patients were randomized to receive G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF), or no colony-stimulating factor (CSF). When given on day 4 of induction until return of absolute neutrophil count of 1000/mL, patients receiving G-CSF had significantly shorter hospital stays, a shorter time to neutrophil recovery, and fewer severe infections as compared with patients who did not receive G-CSF. The CALGB 9111 trial highlighted the benefit of using this drug in patients prone to have difficulty with hematologic recovery, specifically older patients. The study observed a trend toward increased CR rates in patients 60 years or older in the G-CSF arm compared with the placebo arm. In pediatric patients, growth factor use is generally limited to situations involving serious postinduction infections or, in some protocols, routinely after the highest intensity block treatments.

All blood products should be irradiated prior to SCT to prevent alloimmunization. Other important supportive care measures include the use of indwelling catheters, amelioration of nausea and vomiting, pain control, and continuous psychosocial support for the patient and the family.

Toxic complications during chemotherapy

With improving long-term survival in ALL, the focus on toxicity has increased. Toxicity reporting is problematic and has not been uniform across protocols. Recently, consensus-definitions across pediatric study groups were described for 14 common toxicities: hypersensitivity to asparaginase, hyperlipidemia, osteonecrosis, asparaginase-associated pancreatitis, arterial hypertension, posterior-reversible encephalopathy syndrome, seizures, depressed level of consciousness, methotrexate-related stroke-like syndrome, peripheral neuropathy, high-dose methotrexate-related severe nephrotoxicity, sinusoidal obstruction syndrome, thromboembolism, and *P jirovecii* pneumonia infection.

Asparaginase is considered an essential chemotherapeutic drug in many protocols but requires attention with respect to toxicity management, particularly of pancreatitis and thrombotic events linked to deranged coagulation parameters. Abdominal pain or pronounced discomfort after asparaginase should prompt consideration of pancreatitis and testing of lipase and amylase, followed by imaging studies if these enzyme levels are clearly elevated.

Coagulation disorders, mostly attributed to asparaginase, are more frequent and clinically threatening in adults than in pediatric patients because these disorders may lead to sinus vein thrombosis, portal vein thrombosis, or other thromboembolic complications. Vigilance is thus necessary, but clinical practice varies, and there is no consensus on preventive measures.

Late effects

Patients who experience many of these acute toxicities will have long-term side effects, for instance, osteonecrosis, associated with high doses of glucocorticoids. Longer continuous use of dexamethasone especially may lead to permanent joint damage and the need for arthroplasty. A recent study indicates that extended use of asparaginase may also enhance this necrotic effect. Acute asparaginase-associated pancreatitis can also cause long-term effects, such as insulin-dependent diabetes, pseudocysts of the pancreas, and exocrine pancreatic insufficiency, in about a third of the acute cases. Several of these toxicities affect central and peripheral nervous function and, even if many of these are usually transient, sequelae with permanent focal deficits, as well as cognitive impairment, may remain.

Other effects may not be noticed following an acute complication. High cumulative doses of steroids also result in a significantly increased incidence of osteoporosis, which may affect management. It is important to identify any osteoporosis early so that therapeutic intervention and advice on physical exercise to prevent fractures can be implemented. Treatment with anthracyclines, particularly high cumulative doses, can produce severe cardiomyopathy, which may be persistent and progressive years after anthracycline therapy. In current clinical trials, only limited doses of anthracyclines are used, even for high-risk cases, to decrease the risk of subsequent cardiomyopathy; anthracycline-free regimens have also been tried for lower-risk patients.

Cranial irradiation has been implicated as the cause of numerous late sequelae in children and is one of the main reasons to reduce or omit this modality, particularly for younger children. Late effects include second cancers, neurocognitive deficits, and endocrine abnormalities that can lead to obesity, short stature, precocious

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puberty, and osteoporosis. In general, these complications are seen in girls more often than in boys, and in young children more often than in older children. A long-term follow-up study of survivors of childhood ALL revealed a >10% cumulative risk of second neoplasms at 30 years and a higher-than-average mortality rate among patients who had received cranial irradiation. The most devastating complication is the development of malignant brain tumors. The median time to the diagnosis of secondary high-grade brain tumor is 9 years, and the median time to diagnosis of meningioma is 20 years. Although neurocognitive problems are linked to cranial irradiation, they also can be caused by systemic and intrathecal therapy. However, irradiation-induced damage has generally had more pronounced effects in comparative studies. Knowledge of potential treatment sequelae that allows modification of treatment strategy and of appropriate screening measures to permit early detection of complications should greatly improve the quality of life of survivors of ALL.

Mature B-ALL (Burkitt lymphoma/leukemia)

It is critical to differentiate between mature B-ALL and B-cell precursor ALL as treatment is different and BFM-type regimens are not effective in mature B-ALL. The distinction is suggested cytologically by the presence of the so-called L3 morphology with basophilic, vacuolated lymphoblasts and confirmed by flow cytometry. As genetic features, biology, and treatment of mature B-ALL and sporadic Burkitt lymphoma are nearly identical, these entities are discussed together in a separate chapter on aggressive lymphomas.

Lymphoblastic lymphoma

Clinical presentation

Lymphoblastic lymphoma is an aggressive neoplasm of T and B-cell progenitors that represents ~2% to 3% of adult and pediatric non-Hodgkin lymphomas. It shares many features of ALL but is arbitrarily distinguished by bone marrow involvement of <25%. A precursor T-cell immunophenotype accounts for >90% of cases, with antigen expression profiles that may more closely resemble those of late-stage intrathymic T cells than those of T-ALL.

A large mediastinal mass is present in about 90% of cases of T-LBL but not in B-LBL. It may constitute a hematological emergency with superior vena cava syndrome, upper airway obstruction, and pericardial or pleural effusions which may be accessed for immunophenotyping. Other frequently involved sites include lymph nodes, skin, bone, gonads, liver, and spleen. CNS disease is more frequently found in patients with bone marrow involvement and may be a site of relapse. Low-level bone marrow involvement (minimal disseminated disease, MDD) has been associated with a worse prognosis in some pediatric studies.

Molecular markers

A high frequency of mutations of *NOTCH1* and *FBXW7* genes was found in pediatric T-LBL and was suggested to be a genetic prognostic indicator for T-LBL. Superior survival associated with mutated *NOTCH1/FBXW7* was seen particularly in the absence of *RAS* or *PTEN* abnormalities. A 4-gene oncogenetic classifier based on *NOTCH1/FBXW7* mutations and RAS or PTEN alterations was found to be an independent prognostic indicator in adult T-LBL in the GRAALL-LYSA LL03 study.

Therapy

Staging by computed tomography (CT) and positron-emission tomography (PET) is used to confirm initial sites of disease, and magnetic resonance imaging is employed to assess suspect involvement of bone, brain, or heart. Standard treatment is very similar or the same as for ALL, including supportive therapy and special attention to prevention of tumor-lysis syndrome. To reduce the high rates of mediastinal and CNS relapse, pediatric or pediatric-inspired protocols with intensified chemotherapy and emphasis on high doses of antimetabolites are the mainstay of treatment. Rigorous CNS prophylaxis is essential and based increasingly on intrathecal chemotherapy. There is no convincing evidence that either allogeneic or autologous SCT is superior to intensive chemotherapy. Allogeneic SCT may be considered in high-risk or advanced disease, but patient numbers are too small for any clear recommendation.

Mediastinal irradiation

Mediastinal irradiation has been eliminated from pediatric protocols and has failed to reduce the high rate of mediastinal relapse or improve OS in adults. Whereas the routine use of MRT no longer appears necessary with pediatric-inspired intensive regimens in adult patients, its use in adult patients with a residual mediastinal mass is controversial. Use of PET imaging to identify viable residual mediastinal tumor as an indication for MRT has not led to improved survival. Most importantly, systemic chemotherapy should be delivered as planned.

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Novel therapies

Immunotherapy

Antibodies and ADCs

Most monoclonal antibodies in clinical development target the main B-cell differentiation antigen CD19, CD22, and CD20, but CD38 has also attracted attention. The infrequent expression of CD25 and CD123 in ALL makes them targets in only selected subsets of ALL, targeting these specificities is unlikely to play a major role in the future of ALL. Antibodies bound to different cytotoxins have greater potential for efficacy than most naked antibodies and numerous trials with ADCs are ongoing or have been completed in adult ALL. Different design of these ADCs conveys properties that may provide advantages over current agents, such as less hepatotoxicity and VOD with an anti-CD22 ADC that links to a pyrrolobenzodiazepine dimer toxin instead of calicheamicin used with INO. There is also hope that effective CD19-targeting therapies, such as ADCT-402, will provide greater ease of administration than blinatumomab by allowing intermittent versus continuous infusion). Determining the safety and efficacy of these new monoclonal antibodies will require additional clinical trials.

Until recently, antibody-based strategies applicable to T-lineage ALL have been lacking. Daratumumab is a naked human anti-CD38 monoclonal antibody approved for myeloma which, alone and in combination with vincristine or steroids, has shown promising antileukemic effects in relapsed/refractory T-cell and CD38-positive B-lineage ALL including complete remissions by MFC. The combination of daratumumab with nelarabine also holds promise for patients with relapsed/refractory T-ALL. Effectiveness and safety of daratumumab is being further investigated in pediatric and young adults with relapsed/refractory precursor B-cell or T-cell ALL (ClinicalTrials.gov identifier: NCT03384654).

Resistance to blinatumomab and other immune-mediated treatment approaches has been partly attributed to the immunosuppressive activity of regulatory T cells. This mechanism of resistance suggests that the combination of blinatumomab with checkpoint inhibitors may overcome the suppression of T-cell proliferation and restore antileukemic activity of antibody therapy. Early phase studies have evaluated the combination of blinatumomab with programmed cell death (PD)–1 inhibitor nivolumab and the cytotoxic T lymphocyte–associated protein (CTLA)–4 inhibitor ipilimumab, with promising results. Various clinical trials evaluating checkpoint inhibitors in ALL in addition blinatumomab in relapsed/refractory as well as in the frontline setting are underway (ClinicalTrials.gov identifiers: NCT02879695 and NCT03160079).

T-cell engagers (BiTE, TRiKE, DART, etc)

An increased understanding of the mechanisms of resistance to T-cell engagers and improved technologies in designing this type of agents has provided the basis for developing a large spectrum of refined and novel T cell–engaging therapeutic agents that integrate various immune functions into 1 molecule or a single cellular vector. Examples include novel bispecific antibodies combining CD3-directed specificity with targeting of a non-ALL–typical antigen such as CD123 (XmAB14045), simultaneous multiple interaction T-cell engagers (SMITEs), trispecific killer engagers (TriKEs) and bifunctional checkpoint-inhibitory T-cell engagers (CiTEs). In the leukemia space, initial trials of these combinatorial constructs have started mostly in AML.

Novel dual affinity retargeting (DART) proteins are modifications of classical BiTEs that have been successfully applied for the retargeting of natural killer (NK) cells or T cells toward malignant B cells. These DART molecules are bispecific diabodies composed of 2 Fv chains and have more favourable structural and biological properties than BiTEs, resulting in enhanced cytotoxicity compared with BiTEs in preclinical models. Several members of this class of drugs have entered clinical trials, eg, the anti-CD19–CD3 DART duvortuxizumab, also known as MGD011. DART molecules can also be modified to have a longer half-life than blinatumomab, thereby enabling more convenient intermittent dosing.

Another interesting strategy at the interface of BiTE and CART technology is represented by BiTE-expressing chimeric antigen receptor T cells (CART.BiTE cells).

Cellular therapy (experimental CAR T cells and TCR-T cells)

Similarly to antibody-based therapy, the majority of cellular therapy clinical trials to date have focused on BCP-ALL because a panel of B cell–specific differentiation antigens can be targeted without incurring excessive toxicity in other tissues. Besides CD19 as the main target antigen for chimeric antigen receptor T cells (CART) therapy, CD22-directed CAR T cells have been tested and shown to induce remissions in patients in whom previous CD19 CART therapy had been unsuccessful. As in the case of CD19 CAR T cells, downregulation of the target antigen by a variety of mechanisms has been associated with loss of response, although disease recurrence not linked to CD22 antigen loss or mutation has been observed.

Because antigen loss as an important resistance mechanism, research groups are developing dual-target CARs

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that target CD19 simultaneously with another antigen such as CD22 or CD20. Variations to this approach include bicistronic CART targeting CD19 and CD22 simultaneously or creating CAR products with 3 different populations of CAR T cells (anti-CD19, anti-CD22, and anti-CD19-22). Other dual antigen CAR T-cell constructs under development for ALL include a dual CD19 and CD123 targeting CAR and CART therapy targeting 3 targets—CD19, CD20, and CD22.

The complexity and logistical challenges of manufacturing autologous CAR T-cell products and the ensuing delays in delivering treatment to the patients have prompted development of allogeneic "off-the-shelf" therapies, which still face substantial challenges In terms of risk of graft versus host disease (GVHD) induction and rejection by the host. Deletion of T-cell receptor components by gene editing to prevent GVHD or use of CAR-NK cells as off-the-shelf products is under investigation in numerous clinical studies.

Small molecules

Proapoptotic BH3-only molecules

The B-cell lymphoma 2 (BCL-2) protein family regulates the intrinsic apoptosis pathway via direct interactions between pro- and antiapoptotic proteins, with evidence for dependence on both BCL-2 and BCL-XL in ALL. Preclinical evidence indicates that the selective and orally bioavailable BH3-mimetic inhibitors of BCL-2 venetoclax (approved for patients with chronic lymphocytic leukemia and acute myeloid leukemia) and BCL-XL/BCL-2 navitoclax have antitumor activity in ALL and may act synergistically in combination. As a single agent, venetoclax has shown clinical activity in patients with relapsed/refractory early T-cell precursor ALL (ETP-ALL). Based on the concept that dual targeting of BCL-2 and BCL-XL would enhance apoptotic cell death of ALL blasts, a phase I study examined venetoclax in combination with low-dose navitoclax and chemotherapy in pediatric and adult patients with relapsed/refractory ALL or LL with promising preliminary results. The complete remission rate in heavily pretreated patients, including patients who had previously received HSCT was 60%, with delayed hematopoietic recovery as the primary safety finding. Promising efficacy and tolerability data suggest that the venetoclax-navitoclax combination should be explored in high-risk patients with less advanced disease. A related combinatorial approach using BH3-only inhibitors of BCL-2 and MCL1 have shown synergistic efficacy in preclinical models of high-risk human B-ALL. In Ph^+ ALL the combination with TKI likewise proved effective.

The portfolio of novel agents to treat T-ALL has lagged behind those for B-lineage ALL. Among several potentially active small molecules, NOTCH1 inhibitors have attracted the most interest because of the central pathogenetic role of activating NOTCH1 mutations in leukemogenesis. Clinical results have been mostly disappointing, with management complicated by associated gastrointestinal toxicity and lack of efficacy in relapsed patients with highly proliferative disease. Mitigation of gastrointestinal toxicity by dexamethasone and testing during earlier stage of disease may enhance the efficacy of this class of drugs. Because many of the signalling pathways that are aberrantly activated in T-ALL (JAK-STAT, Ras, PI3K-AKT) are targetable by small molecule inhibitors approved or under investigation for other indications, repurposing of these drugs warrants assessment in clinical trials. Based on the high frequency of epigenetic alterations in T-ALL, a number of epigenetic modifying agents have been studied in preclinical models, including DNA methyltransferase inhibitors, HDAC inhibitors, IDH1 and IDH2 mutant inhibitors, BRD4 inhibitors, and DOT1L inhibitors.

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